

Is the End of the Strategic Balance in Sight ?

THERE are signs that the strategic doctrines by which the United States and the Soviet Union have kept each other at bay since the late 1950s are nearing their end. It is several months now since the doctrine of mutual deterrence was repeated in official language—a significant omission at a time when the Department of Defense in the United States is fighting to get its annual budget through Congress. The most suggestive straw in the wind, however, is the appointment of Dr Charles Ikle, now a sociologist with the Rand Corporation, as head of the United States Arms Control Agency. Dr Ikle is a distinguished academic, but, more significantly, is one of those who have been urging that the United States should try to define a military strategy different from the doctrine that potential enemies must be made to realise that military adventures are unthinkable—rashness would invite all-out retaliation and an entirely unacceptable level of damage. It is unlikely that any United States President, but President Nixon least of all, would agree to appoint a director of the United States Arms Control Agency if his views were unacceptable. So the question arises whether a departure from the doctrines of mutual deterrence is to be welcomed or feared.

First, however, it must be acknowledged that the US Arms Control Agency is no longer what it used to be. In 1961 it was intended as the chief workhorse of President Kennedy's determination that genuine measures of disarmament and arms control should be made to see the light of day. Its achievements have been considerable for the first few years of its existence. The agency, small though it may have been, turned out to be a powerful means of holding the ring between the familiar vested interests in the United States—chiefly the Department of Defense and the State Department, with organizations such as the Atomic Energy Commission looking on. Since the resignation of Mr C. C. Smith last year, however, the agency has been without a director and it has become plain that the agency was in for a hard time.

Dr Ikle's appointment does at least suggest that the agency will survive, which is something to be grateful for. Its shrunken budget also implies that the Administration is planning to concentrate some of the functions of the agency in the White House, where the ubiquitous Dr Henry Kissinger functions. And although nobody would dispute that Dr Kissinger would make an excellent director of the Arms Control Agency if he had the time, can the Administration be so sure of itself that it can now safely dispense with allies in one of the few good causes which has a chance of yielding benefits in the next few years?

The proposal that the doctrine of mutual deterrence should now be modified is intricate, and calls for wide debate. There are arguments on both sides, and nobody would pretend to know for sure how they should be weighed against each other. The present doctrines have their origin in the cold war of the 1950s and were the chief contribution of the United States. The argument then was that the capacity to threaten widespread destruc-

tion of Soviet cities was the most practical—even the most economical—way of inhibiting even conventional military adventures. Over the years, the Soviet Union has equipped itself with the means of replying in kind. For much of the 1960s, the "balance of terror" was complete and convincing to both sides.

So why should there now be a change of strategy? It is fair to say that the Soviet Union has never been entirely convinced and has kept adding to its stock of conventional weapons, airborne and naval. No doubt the United States has also been dismayed that the existence of potentially overwhelming weapons has uncomfortably frozen situations in which conventional warfare might previously have been possible—Vietnam is an obvious example, but the invasion of Czechoslovakia in 1966 was a reminder of how the political situation in Europe has been frozen by the existence of nuclear weapons. But there is now no chance that a modification of the nuclear strategies will ever again make it appear simple to settle political differences by conventional wars—and most people will be glad of that. What has changed, however, is the accuracy of missiles. Mutual deterrence depends on one power's confidence in its capacity to retaliate being unharmed by the fear that its adversary might launch an unexpected attack. As things are, it is unlikely that enough is known of the exact positions of missile silos, and that the other side's weapons are sufficiently accurate for that to be an immediate possibility. That is at least one component of the argument in favour of a less rigid reliance on all-out retaliation.

Another incentive for the consideration now apparently being given to the changing of nuclear strategy is the possibility that familiarity with nuclear weapons may make the threat of all-out retaliation less credible than it has been in recent years. If, for example, it is possible in future for one super-power to destroy, say, half the other's missiles, the nation attacked might decide to negotiate, not retaliate. Or that is what the aggressor might calculate—a more alarming possibility. But a more varied strategic armoury would give both sides more options. To that extent a less complete reliance on mutual deterrence would be a benefit.

The most convincing case for a broadening of the strategic policies now followed by the Soviet Union and the United States is, however, the prospect that there may be in the next few years some further benefit from the long-drawn out SALT negotiations on the limitation of strategic weapons. There is even a possibility that the numbers of strategic weapons actually deployed may eventually be so markedly reduced that the threat of being able to inflict overwhelming damage on the other side may be reduced to the point of incredibility.

But there is a sense in which the credibility of the policies of the past few years has stemmed from the way in which the theory of mutual deterrence has been argued widely in professional circles and in public. If indeed there is now to be a change—and there is no



reason why present theories should be frozen indefinitely—it is imperative that these changes should also be argued in public. It may be anomalous that the head of a disarmament agency should be involved in the public justification of a new defence policy but that will have to be Dr Ikle's function. And, of course, it would be unreasonable to expect that any changes there may be could become apparent in the near future.

AID on the Increase

THE report of the panel on the use and practice of Artificial Insemination by Donor* which was set up by the British Medical Association's Board of Science in 1969 is to be welcomed. It is now thirteen years since Lord Feversham and his committee brought in their report on AID and a great deal has happened in both the legal and medical fields since then. It is also clear that the atmosphere in which the Feversham inquiry was undertaken has now changed and Sir John Peel and his colleagues in contrast to Lord Feversham were under no pressure to recommend that AID be banned. As it turned out Lord Feversham and colleagues recommended that AID should be discouraged but they did not take the further step of recommending that it be declared criminal or prohibited by law.

The wheel has now turned full circle and the basis of Sir John Peel's recommendations is that AID should be allowed and that it should be provided free under the National Health Service. Perhaps this is bowing to the inevitable, for although Lord Feversham was able to say categorically in 1960 that AID was not carried out in National Health hospitals, the same cannot be said today. Seven members of Lord Feversham's committee recommended that there should be no change in the laws of legitimacy to accommodate the birth of a child conceived by artificial insemination thus making the child illegitimate. But now, quite properly, Sir John Peel's panel comes out strongly in favour of changing the laws relating to legitimacy so that such a child would be legitimate. In so doing the panel gives support to the two dissenting members of Lord Feversham's committee, who although not wishing to encourage AID felt that the child should not have to bear the stigma of illegitimacy. But what is the demand for AID? Some 1,400 marriages a year are childless because of the husband's infertility, according to Sir John Peel's panel, but other estimates put this number as high as 4,000 marriages a year. Very few of these couples now have children by AID but as fewer children are now available for adoption, the case for AID becomes stronger. There is also a smaller, but even more necessary, demand for AID in cases where it would be inadvisable for a husband to father a child when for example the husband suffers from a particularly debilitating disease which might be passed on to his offspring.

The state has now been reached where careful consideration must be given to the conditions in which sperm is obtained from donors for insemination. Little attention has been given in the past to test the donor for the presence of genetic or other diseases and personal acquaintance with the donor has been taken as enough evidence of the donor's suitability to donate sperm.

*British Medical Journal Supplement, April 7, 1973.

But with the practice of AID on the increase it must be asked whether this affords enough protection for the mother. It is accepted practice in the United States to pay sperm donors and the practice has recently been reported in Britain. But does the payment of donors throw a new light on the practice of AID? It is well known in the United States that the quality of blood obtained for transfusion depends on whether or not the donor was paid. Could the same happen to the quality of sperm if the practice of AID becomes much more widespread? The practitioners of AID are the first to stress the advantages of the technique over adoption. They point out that in contrast to adoption the mother does carry the child for nine months and a normal mother-foetus relationship develops. But whether AID is provided under the National Health Service or not there is a patent need to clarify the legal situation surrounding children born as a result of artificial insemination by donor. The child so born is illegitimate and the husband who hides the fact by appending his own name as the father in the registry of births is in strict law committing perjury. Surprisingly though it may seem the legal situation of the donor is far from clear—does he have the same responsibility in law as the father of an illegitimate child and also can the child lay claim to the estate of the donor? Whether or not AID is provided under the National Health Service in Britain it must be accepted that the technique is proven and will continue to increase in popularity. But the legal anomalies surrounding AID must be removed as soon as possible.

100 Years Ago



AN Icelandic gentleman sends to the *Scotsman* an account of the eruption of the Skaptar Jokull in Iceland, which took place in January last. On January 9, about three o'clock A.M., there was observed from Reykjavik a great fire in the E.N.E. The fire shot up like lightning, displaying beautiful evolutions in combination with the electricity above. So bright was it, that during the dark morning hours it was thought it must be very close to Reykjavik. But when daylight dawned, and the mountains could be discerned, a thick and heavy column of vapour or steam was observed far in the background, beyond all the mountains, so that it was clear that it was far off, and, according to the direction, it seemed most likely to be in Skaptar Jokull, the west part of Vatna Jokull—the great waste of glaciers in the east and south of the island. Morning and night this grand display was visible during the 9th, 10th, 11th, and 12th, and during the day the column of steam and smoke stood high in the sky. All agreed that the eruption must be in Skaptar Jokull, and from various observations it was concluded that the position of the crater ought to be between $67^{\circ} 7'$ and $67^{\circ} 18'$ deg. north lat., and $30^{\circ} 45'$ and $30^{\circ} 55'$ west long. from the meridian of Copenhagen. In the east, near Berufjord, some shocks were felt, and fire was seen from many farms. Ashes, too, had fallen over the north-east coast so abundantly that pasture fields were covered, and the farmers had to take their sheep into the huts and feed them.

From Nature, 7, 470, April 17, 1873

OLD WORLD

Lord Bessborough Delivers Several Telling Blows

GOVERNMENT research establishments should not normally undertake repayment work for industry, according to the Committee of Enquiry into the Research Associations which reported this week. Lord Bessborough's committee feels that research associations by their long and intimate contact with industry are better equipped to undertake work of industrial importance than most of the government establishments. (*Industrial Research and Development*, Conference of Industrial Research Associations, £3.00.)

But even where the work requires equipment and expertise not found within the appropriate research association so that the only appropriate place to do the research is a government establishment, the committee says that the research association concerned should be brought into the management of this activity. The committee is particularly concerned about the role that the Atomic Energy Research Establishment at Harwell is now playing in undertaking contract research for British industry and it suggests that the establishment should be subjected to greater control.

It is clear that Lord Bessborough and his colleagues would prefer to see Harwell converted into a large research association but they reluctantly admit that such a conversion "would be cumbersome". It would be preferable they say, to break the establishment down into "separate research association-type units". Alternatively the facilities at Harwell could be transferred to existing research associations. But Harwell is not the only government establishment to come under attack, and the management of the ship division at the National Physical Laboratory appears in a far from good light. The British Ship Research Association carries out its ship towing work at the ship tank at the NPL, and, according to the report, "the relatively uncoordinated way" in which NPL conducts its ship tank work makes "BSRA's planning, programming and project control very difficult".

The solution, according to Lord Bessborough is for the management of the ship tank to be transferred from the NPL's hands to BSRA. This, according to the report, would be in "the best national interest", but a merger of BSRA into NPL, which has been suggested in the past, would not be desir-

able. It is argued that as the research association's chief interest is to serve their industry and as the NPL's objectives are to serve "more loosely defined national requirements", marriage of the NPL and BSRA would not be effective. But it is, perhaps, the shipbuilding industry's reported wish not to be buried within a national laboratory that carried most weight with the committee.

The committee comes out in support of the customer-contractor principle but it feels that it is not wise to "carry a general principle to an extreme". Support is also given to the government's decision, made last autumn, to abolish the grant-in-aid system to research associations, although the committee recognises that this will put several research associations under financial pressure. A general grant, according to the report "can insulate the recipient from commercial pressures and lead to a lack of initiative and commercial enterprise." In the same context the committee welcomes the recommendation made by the Select Committee on Science and Technology in their third report last year that contracts between industry and

government research establishments should not be subsidized out of public funds.

The report recognizes that to substitute fees for contract research for the sums presently received as a grant is not going to be satisfactory for the associations and it recommends that the government should continue to contribute monies other than for contract work.

Lord Bessborough also says that if more had been invested in research and development in the "bread and butter" industries rather than in "glamorous high technology", then "perhaps our balance of payments history and recent economic progress might have been considerably improved".

The committee feels, however, that the research association systems is easily justified. In 1970 the research associations spent £17 million supporting industrial technology, which is about 2.5 per cent of the amount spent within private industry on research and development. The government contributes £4 million a year to the research associations, which is 0.7 per cent of its total expenditure on research and development. Neverthe-

EUROPEAN RESEARCH

Advice for the European Commission

THE first meeting of CERD, the European Commission's unofficial advisory body on all matters scientific, went off last week with a lengthy discussion on the committee's objects and a convoluted attempt to define pure and applied research.

The twenty-one man committee, whose membership includes scientists, industrialists and representatives of research councils, all of whom are there in their own right rather than as representatives of their governments, is to advise the commission on all matters relating to research and development that fall within the commission's scope. The committee's opinions will be canvassed before the commission officially formulates its policies, and meetings will take place at least twice a year and more frequently if necessary.

Last week's meeting was judged highly successful in Brussels, although differences in approach, ranging from the Rothschild-like theory that research should only tackle specific problems to the more European line that an overall science policy should be created, had to

be ironed out. The meeting ended with each country retiring to decide which areas are in need of research and their proposals will be discussed at the next meeting of the committee. The British members of CERD are Sir Brian Flowers, Chairman of the Science Research Council, Dr John Kendrew, MRC, Cambridge, and Lord Kennet. The committee's chairman, at least until the commission appoints a full-time scientific adviser, is Professor Hendrik Casimir, Director of Philips and the commission's current scientific adviser. Other members of CERD are: Barry, V. C. (Dublin), Bertin, J. (Plaisir, France), Bölkow, L. (Munich), Braans, C. M. (Jutphaas, Holland), Caracciolo di Forino, A. (Rome), Danzin, A. M. (Versailles), De Gennes, P. G. (Orsay, France), Della Porta (Milan), Demeester, M. (Brussels), Janssen, D. (Brussels), van Lieshout, R. (Hague), Lüst, R. (Munich), Metz, P. (Luxembourg), Peccei, A. (Rome), Rasmussen, P. N. (Copenhagen), Weissmermel, C. (Frankfurt), Winterfeld, K. E. (Lyngby, Denmark).

less, according to the report, "overall, the money devoted to research associations has produced handsome benefits for industry and the economy".

The organization of food research in Britain also comes in for attack. The committee points out that there is no overall view taken by the government of food research activities and that there are no formal means of communication between the food research associations and government, Agriculture Research Council stations and the universities which are involved in food research. This has led to duplication of effort and overlap of research. The food research associations also complained to Lord Bessborough of a "lack of openness" on the part of government stations. The committee of enquiry suggests that all basic work done on food research at government and other institutions should be fed to the industries through the research associations.

The ARC spends about £18 million a year while the food research associations in 1970-71 spent only £365,000. ARC representatives sit on certain research association bodies but reciprocal arrangements are rare. The report even goes so far as to state that friction exists in some cases between the research associations and other institutes involved in food research. In spite of all these apparent disadvantages the committee reflects that it is the research associations rather than the ARC "which are more directly meeting the needs of the consumer".

EUROPE

Mergers Good and Bad

THE recent decision to merge the two nuclear power consortia in Britain was a move that will not benefit Europe, according to Mr Christopher Layton, lately *chef de cabinet* to Mr Altiero Spinelli, one of the Italian European commissioners, and now Director for Advanced Technology Industries at the EEC commission. Mr Layton was addressing a conference last week at the University of Sussex on cooperation in research and technology in Europe.

It would have been much better, said Mr Layton, if the British consortia had separately merged with other European nuclear power companies. If they had done so the Central Electricity Generating Board would not have been faced with the prospects of buying British or foreign—a choice that is now inevitable. Instead, it could have chosen between the rival claims of two companies each of which would have had a strong British representation.

Mr Layton came out strongly in favour of wholesale mergers of European companies in order that European industries can effectively compete with

companies in the United States and other parts of the world. In particular, Mr Layton thinks that there should be two strong computer companies in Europe. Siemens and Philips will soon bring out a common range of computers but ICL will not join with these companies because it has "a different philosophy". But the EEC would like to see ICL find a partner in Europe, and Mr Layton suggested that Nixdorf, the German company, might be suitable.

But computers and nuclear power are not the only fields where Mr Layton wants a few strong European companies, and he also mentioned the aircraft industry—"we've got Concorde and we cannot go on like that"—telecommunications, railways and the heavy electrical industry. But Mr Layton was not clear whether the EEC policy is to encourage one or more large companies within Europe in any given industry. In some fields it might turn out to be essential to have only one consortium to compete effectively with companies in the United States. It might turn out that this is essential in the computer industry but first Mr Layton would like to see two companies set up.

Euratom came in for some severe criticisms at the conference. First, Mr Layton said that much of Euratom's programme had failed and then Professor Christopher Freeman, of the Science Policy Research Unit at the University of Sussex, said that there was "clear evidence of considerable doubt" with the performance of this organization. Eldo was also criticized by Professor Freeman but he was loud in his praise of CERN. The success of CERN can be directly attributed to the fact that the organization and the users worked closely together. In fact, said Professor Freeman, an analysis of the success and failure of twenty or so European collaborative ventures in research has shown that no project can hope to be successful without it having a well defined objective and without it having a market for its end product.

Professor Freeman spent some time in detailed criticisms of the work of the MIT team on modelling the environment and economic conditions of the world. In spite of the detailed disagreement between him and Professor Dennis Meadows and colleagues, Professor Freeman stressed that mathematical simulation models are useful research tools and that where he diverges from the conclusions of the MIT team is in thinking that such models cannot as yet be used as guides for science policy.

But it was clear from the conference that the strong national feelings within the European Economic Community have not been removed by these countries signing the Treaty of Rome and that a lot more than legal pressure is needed to break down these barriers.

ENVIRONMENT

European Cooperation

CLOSER cooperation on European environment policies and a work list for the Council of Europe emerged from a meeting of 17 West European environment ministers held in Vienna recently. At the end of the meeting at which 23 countries, some of them non-member states of the Council of Europe, discussed ways and means of preserving the natural environment, resolutions were passed calling for a greater exchange of information between member states. "Close cooperation between governments is necessary in relation to national environment policies in Europe, and legislative and administrative actions and controls should be harmonized wherever possible," the ministers said.

The ministers also resolved to avoid duplication of work on the natural environment by examining the studies that are already being run by international organizations.

They also asked the Council of Europe to look into the possibility of drawing up a legal instrument to define the rights of the individual to an improved environment and to define his responsibilities within it.

Three formal resolutions were drawn up dealing with the management of the natural environment, the conservation of flora and fauna and the dissemination of information about the environment. All three involved work for the Council of Europe.

Lists of endangered species will have to be drawn up and the council will undertake specific studies of areas such as the Mediterranean. At the end of the meeting, and under considerable pressure from Mr Geoffrey Rippon, Britain's Secretary of State for the Environment, the ministers agreed to meet in Brussels in 1975 and in Switzerland at a later date to review progress towards a European conservation policy.

Stoned in Brussels

BRITAIN may be in Europe and the European Commission may be furiously "harmonizing" everything in sight, but language remains obstinately unharmonizable. At last week's meeting of CERD (see page 427) one of the German delegates, speaking in his own language, inserted an aside to the effect that "Einstein war ein grosser Forscher" (Einstein was a great research scientist) which the French interpreter stolidly translated as "Une pierre était un grand chercheur". The non-German speaking French delegates looked a trifle blank.

NEW WORLD

United Nations' Science Policy Checked

by our Washington Correspondent

Two years ago, the Economic and Social Council of the United Nations established a high level committee to plan and coordinate UN policies for bringing science and technology to bear on the problems of developing countries. Called the Committee on Science and Technology for Development, it was launched in the hope that it would provide a strong and effective voice in the development of UN science policy. But that hope dimmed a little last month when the committee's first meeting got bogged down in a political dispute, failed to tackle most of the items on its agenda and ended in uproar.

Although the political problems which dominated the committee's first meeting could have been predicted in advance, the fact that they squeezed out discussion of virtually everything else came as a bitter blow to several participants at the meeting. In short, the committee got caught up in the broad debate about financial aid to developing countries and, as one delegate put it last week, it provided a forum for "national posturing".

The essence of the debate was that delegates from the developing countries insisted that the committee should concern itself first with the adoption of a resolution calling for specific funding commitments from the developed nations. Those delegations, led by Brazil and Pakistan, urged the committee to recommend three financial targets to be reached by the end of the decade, namely that the developing nations should spend 1 per cent of their gross national products on science and technology, that the developed nations should spend 0.05 per cent of their gross national products on direct aid for science and technology in the developing nations, and finally, that the developed nations should devote 10 per cent of their national research and development budgets to problems of the developing nations.

The delegations from the developed nations argued, however, that the committee should not concentrate on financial targets, but should be more concerned with specific projects. The discussion of that topic occupied the first two-and-a-half weeks of the three week meeting, and finally it was put to a vote—in itself a highly unusual procedure since agreements at such UN committees are usually reached by consensus. The vote was neatly split with

the delegates from developing nations voting for the funding recommendations, the delegates from Western developed nations voting against them and the delegates from the Communist countries abstaining. Since the developing countries had a majority the resolutions were passed.

Why were attitudes so rigid that the debate was allowed to carry on for almost the whole meeting, finally ending in a vote whose outcome could have been predicted on the first day? The answer can only be found in the context of other UN committees and activities, according to several sources concerned with the meeting.

At centre stage is a document called the International Development Strategy for the Second United Nations Development Decade, a blueprint on international aid during the 1970s which was adopted by the UN General Assembly. The strategy provides for review of its provisions every two years, the first of which is now getting under way in earnest. A Special Committee on Review and Report will meet in the summer to consider recommendations on updating the strategy from several other committees, including the Committee on Science and Technology for Development, and it will send its own resolutions on the strategy to the Economic and Social Council. Ultimately, the General Assembly will consider the resolutions.

The Committee on Science and Technology for Development thus represents part of the first stage in updating the strategy, and the delegates were anxious to establish their national postures so that their views would carry to the next committee layer. According to a member of the UN Secretariat concerned with the science committee, the postures will perhaps soften at each stage of the review, and it is thus simply unfortunate that the committee's first meeting should have provided the forum for such a tactical battle. That viewpoint was confirmed by a delegate from a developing country, who preferred not to be named, who said that the insistence on funding commitments "was a necessary exercise in the light of the calendar of meetings".

As for the funding targets themselves, the chief bone of contention was the third provision, that the developed nations should spend 10 per cent of their research and development budgets on problems of the developing nations,

drawn up in consultation with those nations. Delegates from the developed countries resisted the proposal for several reasons, only one of which is that for some countries it would represent a significant increase over present spending. Perhaps the chief argument was simply that there are no criteria by which to determine what research is of benefit to developing countries.

Dr Frederick Seitz, President of the Rockefeller University and leader of the US delegation, said last week that the discussion over the third target was really "tilting at windmills". He said that he believes that it would be easy to demonstrate that the United States, the United Kingdom and several other Western countries spend at least 10 per cent of their research and development budgets on problems of benefit to the developing countries, but that little thought has gone into drawing up the relevant criteria. Consequently, the US delegation offered a resolution, which was finally agreed to after revisions, requesting the Secretary-General to convene a group of experts to undertake such a task, and to present its recommendations to the next meeting of the Committee on Science and Technology for Development.

The view of the US delegation, and of most other delegations of the western developed countries, was that in the absence of such criteria it is fruitless drawing up funding recommendations and the committee should concentrate on specific projects. Another member of the US delegation said last week that "if a good project is proposed, money will be found for it".

A member of the British mission to the UN said last week that he was "very disappointed" that little of substance emerged at the meeting, and in particular pointed out that there was no discussion of the future work of the committee, or of its role in relation to other committees of the UN. He added that since the committee got off to such a poor start, many countries may be unwilling to send such top level delegates to future meetings. Dr Seitz was also disappointed at the concentration on funding targets, but said that he was not too surprised at the way things turned out. Nevertheless, "If the next meeting is as fruitless, then I shall be very disappointed", he said.

The delegate from a developing country was more sanguine, however, suggesting that the resolutions on fund-

ing will cause the developed nations to think much more closely about the orientation of their research and development budgets, and will help promote more cooperation between developing and developed countries on science and technology. He added that now the question of funding commitments has been settled, albeit by a vote which did little to change attitudes, the committee can get down to the "more exciting" discussion of projects in its next meeting.

Perhaps the most fitting comment on the meeting was provided not by the delegates, but by the translators. After the meeting had dragged on past the time at which they should have left, the translators walked out, leaving a number of delegates talking in a variety of languages until the chairman finally gavelled the meeting to a close.

HIGHER EDUCATION

Job Prospects Improving

by our Washington Correspondent

THOSE who are about to leave universities in the United States with a first degree will find the job market better this year than at any time in the past four years, according to the latest report from the Carnegie Commission on Higher Education. The commission also believes that job prospects for first degree holders will be fair for the rest of the 1970s and improve in the 1980s. Nevertheless, about a quarter of the new college graduates will find themselves in jobs which have not previously been filled by graduates and of those, about half will have to accept jobs which will not make use of their college education.

The outlook for holders of a PhD is, however, much more grim. The commission reckons, on the basis of a thorough review of masses of statistics, projections and analyses, that the job market for PhDs will perhaps worsen towards the end of the decade and become even tighter in the 1980s. But, while there is likely to be a large surplus in some disciplines, such as the humanities, there may even be a shortage of PhDs in engineering and some of the physical sciences.

The Carnegie Commission's report (*College Graduates and Jobs*, McGraw Hill Book Company, Highstown, New Jersey 08520, \$4.50) presents a vigorous rejection of the suggestion that "man-power planning" should be the basis for planning the development of higher education, suggesting that such an approach is not feasible or desirable in a decentralized economy such as that of the United States. In general, the commission argues that the federal government should not respond to the tight job market of the past few years

by shutting off a variety of student support programmes, and that there is no basis for predictions of "gloom and doom". In fact, the report states that although there will be a temporary glut of graduates in some fields, there will be no "major overall crisis—at least for a long time to come".

The report is the latest in a series of reports and analyses put out by the Carnegie Commission and by a variety of other institutions all of which have been concerned at least in part with one overriding concern—a complex web of factors has created the greatest financial crisis that universities in the United States have ever experienced. Most of the reports have ended up by arguing that changes in attitudes are needed by educators, employers and government officials to cope with the financial crisis and, as far as the job market is concerned, the Carnegie Commission is not alone in recommending against restricting entry into the universities because of a perceived lack of job opportunities for graduates.

In short, what has happened in US higher education is that in the late 1950s and early 1960s the universities underwent a massive expansion, force fed by grants from federal and state governments. Between 1950 and 1970, undergraduate enrolments increased from 2.1 million to 6.8 million, while enrolment for graduate courses shot up from 220,000 to 940,000 in the same period. In most fields the demand for both first degree holders and for those with advanced degrees outstripped supply until a general economic recession set in in the late 1960s.

Partly in response to the high unemployment rate among graduates (which, nevertheless, has remained lower than that of non-graduates) many federal programmes in support of higher education, such as the traineeships and fellowships administered by the National Science Foundation, began to dry up in the early 1970s. Consequently, virtually every university in the United States has been caught in a tight financial squeeze and many have had to cut back on enrolments and staff hiring, and even to drop some courses. And the higher education act amendments, passed by Congress last year, have turned out to be less of a saviour for the universities than many had hoped (see *Nature*, 234, 65, 1971).

What lies in store for those emerging from the universities with newly minted degrees in the next few years? According to the Carnegie Commission, the economic recession is abating and although predictions about the labour market are difficult to make, the United States "appears to be moving towards a favourable employment situation". The report states that the output of college graduates will probably increase

by about 50 per cent on the 1970s compared to the doubling of the 1960s, and the job market should be better than it was between 1968 and 1973, but worse than in the 1960s.

The commission takes note of predictions from the US Bureau of Labor statistics that "a high school education will be sufficient for 8 out of 10 jobs" during the 1970s and points out that in fact one-third of the 18 to 21 age group is in college at any one time. Consequently, the commission reckons that at a very rough guess, between 1 and 1.5 million new graduates will have to take jobs each year for which a college education is not required.

As for the market for PhDs, the slowing down in the growth of undergraduate enrolments and in university expansion in general has already severely cut back on the number of teaching vacancies and other job opportunities in the universities. This trend will continue and will cause severe problems in the PhDs job market in the late 1970s and 1980s, the commission warns.

The report suggests that the universities and state governments should respond to this situation by preventing the spread of PhD courses to institutions that do not now have them and problems in the PhD job market in existing graduate schools should not be started up without good cause.

A task force established by the Department of Health, Education and Welfare, headed by Dr Frank Newman, Director of University Relations at Stanford, also expressed grave concern recently about the recent trends in postgraduate education in the United States, suggesting that the shift in enrolments from institutions of acknowledged excellence to new institutions has given rise to a "threat to the overall quality of graduate training of scholarly research". The Newman task force also suggested that federal cutbacks in training grants and fellowships are hitting hardest in the high quality institutions, thereby tending to reduce overall quality of postgraduate education. The task force's chief recommendation was that postgraduate students rather than universities should be supported by direct, portable grants which they would be free to take to the institution and course of their choice.

As for scientists and engineers, the Carnegie Commission's report suggests that there is a strong possibility that shortages will again develop soon for engineers and graduates in some of the physical sciences. This is partly a consequence of the fact that enrolments have dropped off recently partly in response to the highly publicized unemployment of engineers in industries particularly affected by the economic recession.

NEWS AND VIEWS

More Questions than Answers at East Rudolf

RESULTS of field work in the East Rudolf area of Kenya continue to expand knowledge of the evolutionary development of man, but as Richard Leakey has pointed out in a recent issue of *Nature* (242, 170; 1973), more questions are now arising than are finding answers.

Because of Leakey's insistence on the representation of a wide variety of geological, palaeontological and anatomical specialities East Rudolf continues to be one of the best known early man locales. Even the continuing difficulty in obtaining further reliable radiometric dates has not been a severe handicap because other methods of dating the sites are now available. Maglio's attempt (*Nature*, 239, 379; 1972) to correlate the East Rudolf fauna with that from other radiometrically-dated sites in East Africa seems a particularly good application of a dating method which, in other circumstances, has been justly criticized.

Leakey's report in this issue (see page 447) brings abundant affirmation of the lower Pleistocene (if not Pliocene) existence of the genus *Homo*. The large, and now reasonably complete calvarium, KNM-ER 1470, reiterates what more fragmentary and less dramatic material from the East Rudolf area has been suggesting for some time. The postcranial material, including two nearly complete femora, also re-emphasizes and clarifies the early hominid dichotomy. The comparatively large size of this skull, the lack of strongly developed or continuous brow ridges, the vertical parietals and other morphological features of the cranium quite clearly place the specimen outside the australopithecine grade of evolutionary development. In view of other evidence from past seasons, especially the KNM-ER 730 and 820 jaws and the KNM-ER 737 femur, the early existence of *Homo* at East Rudolf is no surprise. Although no dental measurements accompany this preliminary report it is interesting that the recently discovered "*Pithecanthropus VIII*" skull in Java shows apparently similar mesiodistal compression of the cheek teeth and a short, broad palate as are seen in the new Rudolf skull. The zygomatic process of the maxilla also appears to show a similar conformation in the two specimens.

One of the big bonuses of the East Rudolf material is the collection of associated material—associated in the sense of two or more bones having come from a single individual. Although definitely associated cranial and postcranial material has not yet been discovered at any lower Pleistocene hominid site, several related limb bones are now known from the Rudolf area. The body of evidence now available indicates that australopithecine locomotion, although clearly bipedal, did not necessarily conform to a hypothetical transitional model between apes and man. It now seems possible that the locomotive behaviour of these early hominids may have been different from any known pattern. The suggestion that the forelimb may have been long in relation to the hindlimb is interesting and may stimulate work which will eventually clarify one of the most elusive aspects of studies of early man.

The question which the new material really poses is what should now be done, in a taxonomic sense, with the gracile australopithecine and "*Homo habilis*". "*H. habilis*" has been suggested as a direct ancestor of modern man, yet, more than a million years later than KNM-ER 1470, the habilines from Bed I at Olduvai Gorge have a smaller endocranial capacity and a cranial morphology perhaps more primitive in some respects than the Rudolf skull. Although it is dangerous to put too much emphasis on brain size alone (living *H. sapiens* has a range of more than 1,000 cm³) the quite advanced morphological pattern of the new skull clearly suggests that it is not australopithecine.

It may well be, as Leakey has suggested elsewhere, that the East African material presently suggested to be from gracile australopithecines should be re-allocated. The very wide diversity found in this group would mean that some specimens would be placed with the robust australopithecines and some specimens would be placed with *Homo*. This would clarify and simplify the situation seemingly revealed by the postcranial bones. In the lower limb there is clear evidence of two types of erect and efficient bipedality. But if two types of australopithecines are recognized in East Africa then the mounting evidence of contemporary *Homo* could demand three types of lower limb morphology; this is not indicated in the East Rudolf material.

There is a further and perhaps sometimes overlooked implication of the East Rudolf material. It can no longer be doubted that two types of hominids co-existed in East Africa; if the Chesowanja skull (Carney *et al.*, *Nature*, 230, 509; 1971) is accepted as the latest (and last) evidence of that co-existence then the period of sympatry was at least 2 million years. This firmly and unequivocally indicates that the australopithecines were not incompletely evolved or inefficiently adapted hominids, as some workers have suggested; it is indicative of a very high level of adaptation and development that two closely related hominids were able to co-exist successfully for such a period.

From our Palaeoanthropology Correspondent

"Gating Currents" in Axons

It is generally accepted that the action potential of nerve cells and muscle fibres arises from a transient increase in the ionic permeability of the surface membrane which in turn leads to a transient inward movement of positive ions. Since the pioneer work of Hodgkin and Huxley (1952) the ionic currents have been measured in a variety of experimental conditions; ionic permeabilities and their dependence on voltage and time have been extensively studied. The ultimate aim has been to obtain information

about the events which, on a molecular level, cause the transient increase in membrane permeability. Considerable efforts, both experimental and theoretical, have been made to elucidate the molecular events (see the review by Keynes, *Nature*, **239**, 29; 1972); in spite of these efforts, however, the molecular basis of the permeability changes has essentially remained a mystery.

The characteristic property of an (electrically) excitable membrane is the marked dependence of its ionic permeability upon voltage. The simplest explanation would be that charged particles (for example, the flexible polar ends of certain phospholipid molecules) alter their position in the membrane according to the electrical potential across the membrane, thereby opening or closing pathways ("gates") for ions such as Na^+ or K^+ . This hypothesis has an important consequence: the opening of the ionic "gates" should itself produce a small membrane current which precedes or parallels the sodium or potassium current and is caused by the displacement of the charged particles inside the membrane. This "gating current" should be proportional to the number of "gates" and the amount of charge transferred at each one. Because of its small size it should be seen best in the absence of the normal ionic currents.

The search for the hypothetical "gating current" became an exciting task for axon physiologists. As the years passed by, the hunt grew more and more intense; new methods such as signal averaging and intracellular perfusion of giant axons improved the chances for solving the problem. Chandler and Meves (*J. Physiol.*, **180**, 788; 1965) found no evidence for a "gating current" within the limits of their instrumental sensitivity, whereas unpublished experiments by H. M. Fishman (see footnote in Jain *et al.*, *Proc. US Nat. Acad. Sci.*, **67**, 799; 1970) seemed to indicate a positive result. On page 459 of this issue of *Nature*, Armstrong and Bezanilla describe "currents related to movement of the gating particles of the sodium channels".

Armstrong and Bezanilla used the voltage clamp technique to carry out their experiments on intracellularly perfused squid giant axons. The ionic currents were reduced to a minimum by using a sodium-free external and a potassium-free internal solution. The capacitive and the leakage current were eliminated by algebraically summing the currents from equal pulses of opposite sign. This was done by a signal averager which averaged the currents from several thousand pulses of each polarity. The current remaining after this procedure was a transient outward current at the beginning of the clamp pulses and a transient inward current at the end of the pulses. The current transients (which have a superficial similarity to recently published records from the frog muscle, see Schneider and Chandler, *Nature*, **242**, 244; 1973) are interpreted as "gating currents". This interpretation is supported by measurements of the area under the current transients which, for strong pulses, corresponds to 300 electronic charges per μm^2 of membrane; assuming six charges per gate one arrives at 50 gates per μm^2 , in reasonable agreement with estimates derived from studies of tetrodotoxin binding to other axonal membranes. A great deal more work is, however, required until one can be sure that the current transients described by Armstrong and Bezanilla have something to do with the opening and closing of the "sodium gates".

The experiments of Armstrong and Bezanilla justify

the hope that the problem of the excitable membrane may eventually be solved along the lines that have been indicated. Another report about new experiments on squid axons (see Landowne, on page 457 of this issue of *Nature*) seems more difficult to reconcile with present ideas about the function of the nerve membrane. The voltage clamp studies of Hodgkin and Huxley (1952) showed that low temperature prolongs the duration of the permeability changes without appreciably interfering with the magnitude of the permeability increases; therefore a large increase in the net ionic movement during activity was predicted for low temperatures. The expected increase in potassium loss at low temperatures was subsequently found (Shanes, *Amer. J. Physiol.*, **177**, 377; 1954), but the effect of low temperature on sodium entry was never investigated. The experiments by Landowne are concerned with this question. The results are, however, quite unexpected: they show a clear decrease (rather than the predicted increase) of sodium entry during activity at low temperatures.

There are probably several ways to explain the apparent paradox. Landowne chooses the most radical interpretation by saying that his data "seem to rule out any model of the nerve membrane which accounts for the current by a simple change in permeability". He develops an alternative model based on the assumption that the amount of sodium which enters the fibre during the nerve impulse is limited to the amount of sodium stored inside the surface membrane before the impulse; the amount of stored sodium is assumed to decrease with decreasing temperature (see also Hoyt and Strieb, *Biophys. J.*, **11**, 868; 1971). It is interesting to note that this model does not seem to require the existence of "ionic gates" and "gating currents". The full justification for the far reaching theoretical conclusions is difficult to judge; it seems, however, certain that "Landowne's paradox" will stimulate further experimental work.

H. M.

Neuronal Plasticity

ONE of the most interesting and poorly understood phenomena in neurobiology concerns the nature of neuronal plasticity and of the trophic influences exerted by neurones on innervated structures. Recent studies have revealed that selective changes occur in the synthesis of well-defined macromolecules in adrenergic cells in response to changes in neuronal activity, suggesting that such cells may provide a valuable model for biochemical studies of these processes. It has been found that the activity of cholinergic nerves supplying adrenergic neurones in sympathetic ganglia or adrenal chromaffin cells partially controls the synthesis of the key biosynthetic enzymes tyrosine hydroxylase and dopamine- β -hydroxylase in these adrenergic cells (for review see Molinoff and Axelrod, *Ann. Rev. Biochem.*, **40**, 465; 1971; Thoenen, *Biochem. Soc. Symp.*, No. 36, 3; 1972).

Neuroblastoma cells, derived from a mouse tumour of adrenergic origin, have been widely used as an *in vitro* model system for studying the factors which control neuronal development and differentiation. Such cells, unlike normal neurones, grow and divide rapidly in tissue culture, although their genetic heterogeneity leads to considerable morphological and biochemical variations among

individual cells. This latter problem has to some extent been overcome by the systematic isolation and analysis of a variety of neuroblastoma of clonal origin (Amano, Richelson and Nirenberg, *Proc. US Nat. Acad. Sci.*, **69**, 258; 1972). Some clones give rise to cells containing extremely high activities of the enzyme tyrosine hydroxylase, and one of these "adrenergic clones" has been used by Richelson (*Nature New Biology*, **242**, 175; 1973) to examine the control of the synthesis of the enzyme tyrosine hydroxylase.

Richelson confirms the previous finding (in a similar but less active neuroblastoma preparation) of Waymire, Weiner and Prasad (*Proc. US Nat. Acad. Sci.*, **69**, 2241; 1972) that the addition of dibutylrly cyclic AMP causes approximately a doubling in the activity of tyrosine hydroxylase. The new study shows, furthermore, that this change in enzymatic activity represents both an increase in the specific activity of the enzyme (per milligram protein) and an increase in the total amount of enzymatic activity per cell. This is an important point, because Richelson also confirms (as reported by Waymire *et al.*, 1972) that sodium butyrate — a possible metabolic product from dibutylrly cyclic AMP — causes an increase in the amount of tyrosine hydroxylase per cell, but not in its specific activity.

Sodium butyrate seems to inhibit cell division. In the normal growth of neuroblastoma cells in tissue culture, formation of the enzyme occurs largely after the log phase of growth is completed; by arresting cell division butyrate seems merely to accelerate the normal processes of biochemical differentiation occurring in the cultured cells. When cells were cultured with reduced amounts of foetal calf serum, so that cell division was not encouraged, butyrate no longer had any effects, although dibutylrly cyclic AMP was still effective. The actions of dibutylrly cyclic AMP were enhanced by the phosphodiesterase inhibitor theophylline. Prostaglandin E_2 , however, which has been reported to increase the concentration of cyclic AMP in neuroblastoma cells, did not cause any marked increase in tyrosine hydroxylase activity. The results, nevertheless, strongly suggest that cyclic AMP may play a part in the biochemical differentiation of neuroblastoma cells, and, by inference, of adrenergic neurones. Addition of dibutylrly

cyclic AMP has also been shown to influence other aspects of the morphological and biochemical specialization of neuroblastoma cells (Prasad and Hsie, *Nature New Biology*, **233**, 141; 1971; Furmanski, Silverman and Lubin, *Nature*, **233**, 413; 1971).

The implications of Richelson's findings in neuroblastoma cultures have been supported by recent results obtained with normal adrenergic cells. Addition of dibutylrly cyclic AMP to organ-cultured mouse and rat sympathetic ganglia leads to increased synthesis of the enzymes tyrosine hydroxylase and dopamine- β -hydroxylase in the adrenergic neurones of these ganglia (Mackay and Iversen, *Brain Res.*, **48**, 424; 1972; Keen and McClean, *Arch. Pharmacol.*, **NS**, **275**, 465; 1972). In such isolated ganglia, the stimulation of tyrosine hydroxylase activity by nerve activity *in vivo* can be simulated by the addition of substances such as potassium chloride that cause a depolarization of the adrenergic neurones. These effects are enhanced by theophylline, suggesting again an involvement of the cyclic AMP system in mediating the control of enzyme synthesis by depolarizing stimuli. Such an involvement is also supported by the finding (Guidotti and Costa, *Science*, **179**, 902; 1973) that conditions leading to increased tyrosine hydroxylase activity in rat adrenal medullary chromaffin cells *in vivo* are

associated with an increase in the concentration of cyclic AMP in such cells. The phosphodiesterase inhibitor aminophylline also promotes an increase in the cyclic AMP content and in tyrosine hydroxylase activity in these cells.

The biological ramifications of the adenylate cyclase-cyclic AMP control system know no bounds. A role in controlling neuronal plasticity, however, is at least a relatively novel regulatory function for this ubiquitous messenger substance.

From our Neuropharmacology Correspondent

GROOMING MOVEMENTS

Endogenous Control

from our Animal Behaviour Correspondent

DURING the past ten years, considerable interest has centred on the effects that various sorts of feedback from an animal's own movements or sounds have on the subsequent development of complex species-specific patterns of behaviour. White-crowned sparrows, for example, need to hear the sound of their own voices if they are to develop the proper song characteristic of their species. When white-crowned fledglings, which have been exposed to their species song, are deafened before they themselves have started singing, they subsequently produce highly abnormal songs (Konishi, *Z. Tierpsychol.*, **22**, 770; 1965). They thus seem to need to hear

Reverse Transcriptase of Chick Cells

IN *Nature New Biology* next Wednesday (April 18) Kang and Temin report new data which add support to their claim to have detected in chick embryo cells an RNA-dependent DNA polymerase; in other words a reverse transcriptase, which is biochemically and serologically distinct from the reverse transcriptase present in avian RNA tumour viruses. Last year Kang and Temin reported (*Proc. US Nat. Acad. Sci.*, **69**, 1550; 1972) that chick cells contain an endogenous reverse transcriptase associated with an endogenous RNA template. They showed that this activity is sensitive to RNase, resistant to DNase, partially resistant to actinomycin D and makes a DNA complementary to the associated RNA. They failed, however, in their initial attempts to isolate a RNA/DNA hybrid intermediate made by this chick endogenous reverse transcriptase.

By varying slightly the method of isolating this endogenous reverse tran-

scriptase activity, Kang and Temin have now succeeded in obtaining preparations which *in vitro* synthesize DNA and give rise to an RNA/DNA hybrid, the RNA moiety of which is sensitive to RNase and alkali and can be heat denatured. Furthermore, they obtained evidence which suggests that the DNA chain of the hybrid may be covalently linked to an RNA primer molecule. These properties of the RNA/DNA hybrid molecules made by this activity are reminiscent of the RNA/DNA hybrids made at early times by reverse transcriptase of tumour viruses, but the endogenous enzyme of chick cells and the enzyme in avian RNA tumour virus particles are different molecules. As Kang and Temin say, these data "suggest that endogenous RNA-directed DNA polymerase activity is not unique to viruses, and virus-infected or tumour cells". What role the endogenous reverse transcriptase of chick cells plays remains a fascinating question.

themselves practising. There are other cases, however, where no such feedback is apparently necessary: chickens deafened soon after hatching give all the normal species calls (Konishi, *Z. Tierpsychol.*, **20**, 349; 1963).

Fentress has now given a particularly clear demonstration of a complicated sequence of movements developing in the absence of obvious feedback (Science, **179**, 704; 1973). The grooming movements of mice are characteristic of the strain to which the mouse belongs and have several definable components which follow each other with a fair degree of regularity. The forepaws sweep over the snout and various parts of the face and contact the tongue in a complex pattern. Mice which have had one or both forepaws amputated at birth so that they have only stumps also "groom": they sit in the hunched posture characteristic of a normal grooming mouse; their tongues, shoulders and stumps move just as if they had functional paws. They show the same increase in amount of grooming that normal mice do during their third week after birth, and the normal coupling between shoulders and tongue movements occurs even though the tongue has no paws to lick. Most striking of all, the shoulder traces out large amplitude sweeps over the eye and the eye closes at just the right time even though there is no paw there to touch it. The sequence of movements is also similar. Normal mice go from licking to single rapid strokes along the snout and the mice with amputated paws also show this transition.

Although there may, of course, be subtle as yet undetected differences between normal and pawless mice, it is clear that what might be thought an essential stimulus, namely, the touch of the paws on the face, is not necessary either for the development or for the execution of a complex series of movements involving several parts of the body.

TISSUE CULTURE

Fun with Cytochalasin B

from our Cell Biology Correspondent

ADDING a dash of cytochalasin B to cultures of mammalian cells and watching what happens seems to have become a diverting pastime for many cell biologists, and there is no denying that this interesting drug causes cultivated cells to undergo remarkable changes. Perhaps the most dramatic and ultimately useful property of cytochalasin B is that it can, when used in appropriate conditions, cause the enucleation of most cells in a population. Goldman, Pollack and Hopkins (*Proc. US Nat. Acad. Sci.*, **70**, 750; 1973), for example, by ingeniously

harnessing centrifugal force with cytochalasin B, have obtained populations of enucleated BSC-1 cells and BHK-21 cells attached to coverslips and their data clearly indicate that these enucleate cells are viable. They can, for instance, be removed by exposure to trypsin solutions from the coverslips and then replated whereupon they resume the typical morphology of cultivated fibroblasts (BHK-21 enucleates) or epithelial cells (BSC-1 enucleates).

Obviously the enucleates must contain whatever information, in other words, molecules are necessary for attachment, spreading and form. The enucleates are also capable of pinocytosis and locomotion; they are susceptible to contact inhibition of locomotion, and Pollack and Goldman have apparently shown that they support virus replication. Presumably, therefore, there is in the cytoplasm of these cells sufficient amounts of the macromolecules involved in these various processes to allow them to continue for several hours after the loss of the nucleus. And one does not need much imagination to devise interesting experiments that exploit that fact. What, for example, happens when enucleate cells are infected with transforming viruses or fuse enucleate cells of one sort or another to nucleated cells using inactivated Sendai virus to mediate fusion? Such experiments should be fun to do and the results may even be rewarding.

Defendi and Stoker (*Nature New Biology*, **242**, 24; 1973) have recently drawn attention to another useful property of cytochalasin B, namely its ability to induce general polyploidy in populations of BHK-21 cells and presumably cells of other lines. Regardless of whether or not the target of the drug is a cells microfilament system, and that is a vexed question, in appropriate conditions it causes the nuclei of BHK-21 cells to divide but prevents cytokinesis, the division of the cytoplasm. As a result binucleates accumulate and when the drug is removed many of these binucleates undergo a further round of DNA replication before mitosis and cytokinesis so that many cells emerge tetraploid. As Defendi and Stoker point out, although many drugs induce polyploidy by interfering with the mitotic spindle cytochalasin B induces polyploidy without drastically reducing viability. It ought, therefore, to be possible to use the drug to induce polyploidy in experiments designed to test how the chromosomal constitution of a cell affects the expression of phenotypic characters. In particular it should be possible to exploit cytochalasin B to test the idea, championed by groups led by Harris, by Pollack and by Sachs, that a cell's chromosome balance regulates its tumorigenicity.

In short cell biologists now have at

hand a drug that can be used to yield viable enucleates or viable polyploids. The bags from such a happy hunting ground should be considerable.

BACTERIA

Colicide

from our Molecular Biology Correspondent

THE colicins are proteins, secreted by strains of *Escherichia coli*, which have the property of rapidly and specifically killing various related bacteria. This phenomenon has been examined at a number of structural and biochemical levels: in the best documented case, that of colicin E3, the site and nature of the lethal act have now been established, and a certain amount is known about how the intruder insinuates itself into the cell. The target of colicin E3 is the 16S RNA of the smaller ribosomal subunit, which it severs near the 3' end, with consequent annihilation of biosynthetic function. There are some odd aspects of this reaction, in particular that the colicin will not attack isolated RNA, or even the lone 30S subunit. This can in principle be explained in terms of ribosomal conformation, which, as a variety of independent lines of evidence suggest, undergoes some sizable change when the subunits dissociate; it has also been suggested, however, that the colicin is not in itself a nuclease, but rather a regulator of a dormant nuclease already present on the ribosome. Some evidence in favour of the first explanation now comes from Dahlberg *et al.* (*Biochemistry*, **12**, 948; 1973).

They find that the cleavage of the 16S RNA by the colicin is subject to inhibition by some antibiotics which are known to operate directly on the ribosome. Thus streptomycin, which binds to the ribosome, deranges the assembly of the polypeptide chain, with apparently an accompanying structural disturbance, will prevent cleavage of the RNA by the colicin in streptomycin-sensitive, but not in resistant cells. Two other antibiotics, which are not thought to have the same ribosomal binding site as streptomycin, function similarly, both *in vivo* and *in vitro*. This argues strongly in favour of stringent conformational requirements that specify the circumstances in which the colicin E3 will interact with the 30S subunit. Dahlberg *et al.* report that the selfsame scission of the 16S RNA occurs also when *Bacillus stearothermophilus* ribosomes are exposed to colicin E3, although the sequence at the 3' end is quite different from that in *E. coli*. This too then apparently reflects a structure-dependent specificity. Two antibiotics, erythromycin and also kasugamycin, which is known to interact with the 16S RNA at the 3' end, that is to say, in the very

region attacked by colicin E3, do not interfere with colicin inactivation.

Confirmation that the attack on the 16S RNA is indeed the lethal event, rather than any action in the membrane, for example, that might precede it, comes from Samson, Senior and Holland (*J. Supramol. Struct.*, **1**, 135; 1972), who find that protein synthesis is arrested some five minutes after the addition of colicin E3 to the culture, and that the cleavage of the RNA, as followed by gel electrophoresis, occurs over about the same period. There is in fact some indication that protein synthesis continues for a few minutes after cleavage, perhaps until completion of the polypeptide chain. A curious observation is that a small amount of the 3' terminal fragment, or at least something indistinguishable from it electrophoretically, appears to be present even in cells that have not been exposed to the colicin.

The other colicins, E1, E2 and K, which are also proteins of about 60,000 molecular weight, do not evidently attack the ribosomes, and may act instead on the membrane. Like E3, they must have the ability to enter the cell, in spite of their large size. Direct observation of some form of mayhem by colicin E1 in the *E. coli* membrane is described by Phillips and Cramer (*Biochemistry*, **12**, 1170; 1973). The fluorescence of the lipid-soluble molecule, anilino-naphthalene-sulphonic acid (ANS) in the *E. coli* membrane is slightly shifted and considerably enhanced on addition of colicin E3, and the same is true of the less polar, and presumably even more lipophilic species N-phenyl-naphthylamine (NPN). The cells can be rescued from the effect of colicins by addition of trypsin within a short period after exposure to the colicin, which is presumably destroyed on the surface before its ingress into the cell. Phillips and Cramer find that the fluorescence enhancement lags behind the absorption of the colicin measured in this way. The colicin E1 induces leakage of potassium and a drop in intercellular ATP concentration. This, however, is not the cause of the fluorescence change, for the perturbation is not affected by prior exposure to a reagent that causes the ATP level to be sustained. The simplest interpretation of these events is that the colicin brings about a cataclysmic change in the membrane when it enters, which affects permeability to potassium ions or ATPase activity.

In an accompanying article, Cramer, Phillips and Keenan (*ibid.*, 1177) adduce more evidence that the fluorescent enhancement of the NPN is a structural effect, for the Arrhenius plot for the kinetics of the increase show a break that corresponds to the temperature of the membrane phase transition to a more fluid state, this depending on the temperature of cell growth, which in turn

governs the phospholipid composition of the membrane. There seems also to be a small change in fluorescence polarization, and hence mobility of the fluorescent marker. The passage of the colicin into the membrane thus seemingly depends on the nature of the bilayer.

The colicins have specific membrane receptors, which evidently participate in their passage through the bilayer, and Sabet and Schnaitman (*J. Biol. Chem.*, **248**, 1797; 1973) have now achieved substantial purification of such a protein. The colicin E3 binding activity passes into a detergent-soluble fraction on disruption of the membranes, and can be further purified by ion-exchange chromatography. Not only does it bind the colicin, but the complex is precipitated by a colicin-directed antiserum. Moreover, the protein is missing in colicin E3-resistant cells. Sabet and Schnaitman estimate that there are some 220 molecules of the receptor per cell. The similarity between the colicins is strikingly underlined by the observation that the colicin E2 binds to the same receptor. Colicins E1 and K, however, do not bind. The receptor activity for these species is also solubilized by the

detergent, but does not remain with the E3 and E2-binding activity after fractionation. There are reasons for postulating that E1-receptor activity might involve the same protein (or actually glycoprotein, for carbohydrate residues are implicated) in combination with some other component.

PLANT GEOGRAPHY

Success and Fall

from our Plant Ecology Correspondent

MUCH effort has been expended on tracing the geographical origins of domesticated plants and animals. Many species have been transported far from the places in which they evolved and their responses to climatic factors have been greatly modified by selective breeding. This makes it difficult to determine their origins from their physiological attributes. Weed species have certain features in common with crop plants; they too have been carried far from their points of origin, often to regions of differing climates. Weeds, however, have not been subjected by man to such rigorous selective pressures

Where the Rhodopsin is Not

A RECENT article by Dratz *et al.* (*Nature New Biology*, **237**, 99; 1972), purporting to show that rhodopsin is completely buried within the rod outer segment membrane has drawn criticisms from Vanderkooi, and a rejoinder from Dratz and Schwartz. In the original article the inaccessibility of the rhodopsin at the aqueous interface of the membrane was inferred by the failure of reactive side chains to react with a covalent labelling compound incapable of penetrating into the bilayer. By contrast, rhodopsin liberated by disruption of the membrane reacted copiously. Vanderkooi points out, in next Wednesday's *Nature New Biology* (April 18), that there could be other reasons for low reactivity than physical occlusion. He notes that other workers have found reagents capable of reacting with rhodopsin side chains in the membrane, supposedly without entering the bilayer. He also draws attention to a large body of X-ray diffraction evidence which is united in the one respect that the rhodopsin is only partly immersed in the membrane, and projects out of it into the aqueous medium.

In an accompanying communication, Dratz and Schwartz reject Vanderkooi's arguments, but not apparently his conclusion that their inferences were wrong. They suggest that published results on specific labelling referred to by Vanderkooi are also ambiguous, because some reagents can penetrate the bilayer and others have a geometry that may

enable the reactive group to project into the bilayer and there react. They then refer to work of their own, and others, given at a recent meeting of the Biophysical Society, which indicates that part of the rhodopsin is in fact available to reagents in the aqueous medium. They have also calculated electron density profiles across the membrane for various dispositions of the rhodopsin, and do not seem to find good agreement with experiment for any of the models, including that for totally buried protein: here the shape is right (which it usually is), but the quantitative fit is poor.

The dispute may help to clarify the limitations in the use of labelling reagent for membrane proteins, includes an implicit admission of error in the earlier work, but makes no impression on the problem of rod outer segment membrane structure.

An article by Phillips and Morrison in the same issue of *Nature New Biology* emphasizes the complexity of reactivity of membrane components. Iodination of red cell membranes under the action of lactoperoxidase leads to labelling of only two proteins, which are therefore accessible at the surface. The new results show that after mild treatment with trypsin, which releases surface glycopeptides, the same two proteins take up much more label. This is interpreted in terms of a protective carbohydrate barrier on the outer membrane surface.

and their physiological requirements can occasionally offer a clue to the climatic conditions and hence the geographical situation of their origins.

Thompson (*Ann. Bot.*, **37**, 133; 1973) has examined the germination characteristics of the weed *Agrostemma githago*, the corn cockle, with the intention of tracing its origin. Thompson has already established that the temperature requirements of seeds for germination vary according to the climatic conditions under which the species evolved (*Ann. Bot.*, **34**, 427; 1970). A surprising outcome of this earlier work was that species of Mediterranean origin germinate at lower temperatures than those from northern Europe, a feature of selective value in a situation where the most unfavourable period for establishment and growth is during the dry, hot summer. Germination in the winter allows establishment to occur well before the physiological stress of summer.

Thompson has found that *Agrostemma* has the germination characteristics of a Mediterranean species; even at 0° C there is moderate germination. Its distribution in Europe is now widespread as a result of dissemination with cereal seed, which it closely resembles in size. Probably its association with cereal cultivation is as old as agriculture itself. Its success as a weed can be associated in part with the germination characteristics which *Agrostemma* had evolved in response to its native Mediterranean climate. It can germinate very early in the spring and soon after ripening. These features, in addition to its very high viability, have made the species a successful opportunist.

In spite of many adaptive features the success of *Agrostemma* as a weed species has declined markedly during the past hundred years. In the nineteenth century the plant was an abundant weed in cornfields in Britain, but by the early part of this century it had become far scarcer. This decline coincides with the introduction of more rigorous screening of cereal grain, which has reduced the likelihood of re-introduction of *Agrostemma* with each year's sowing. This cannot fully account, however, for the virtual elimination of the species. One must also explain its failure to maintain a viable population derived from earlier introductions. Here the Mediterranean adaptations which Thompson describes may once again provide the answer. Germination at low temperature in autumn in British conditions can result in the exposure of seedlings to the severity of winter, which a Mediterranean species is not adequately fitted to withstand. It is ironic that the very characteristics which led to the success of *Agrostemma* may now have contributed to its downfall.

MARS

Polar Wandering?

from our Geomagnetism Correspondent

THE possibility of terrestrial polar wandering (as opposed to continental drift) has been under discussion for many years now, although a firm conclusion one way or the other has yet to be reached. In the meantime, however, Murray and Malin (*Science*, **179**, 997; 1973) are already speculating on the possibility of polar wandering on Mars, on the basis of Martian features revealed by Mariner 9.

What Murray and Malin consider to be the most "suggestive" evidence comes from the quasi-circular topographic features observed in the polar regions of Mars. These features were recently described by Murray *et al.* (*Icarus*, **17**, 328; 1972) as near-circular plates with outward sloping edges and comprising thin (20–80 m) lamellae of light and dark material. Because they form generally concentric patterns and occur only in polar regions, it is tempting to relate their origin and subsequent history to the position of the Martian spin axis, the assumption being that they formed symmetrically about the rotational pole. But what makes them particularly interesting from the point of view of polar wandering is that they seem to form a series of offsets. Thus if the polar origin assumption is valid, the implication is that the poles have also undergone displacement.

The association of the topographic features and their laminated terrain with the poles also implies an association

with the polar carbon dioxide "frost" which appears and disappears on an annual cycle. This, in turn, implies a genetic relationship with volatiles and thus leads to a natural explanation for the polar symmetry. The idea here is that the volatiles may collect atmospheric dust before being lost by sublimation. The symmetry of the topographic features about the spin axis may therefore represent the annual stability boundaries of the volatile carbon dioxide. In other words, the behaviour of the polar-related carbon dioxide appears to leave a visible trace which may be used to determine any polar motion. On this basis, the plates clearly visible indicate a polar motion of about 15°.

A second line of argument is based on the strong evidence for extensive volcanic and tectonic activity on the surface of Mars—in particular, the discovery by Mariner 9 of large constructional volcanic features with a general morphology similar to that of terrestrial shield volcanoes and located near the equator in the longitude range 90°–150° W. The largest of these features corresponds to the previously-known albedo feature Nix Olympica, although three others, about 400–550 km in diameter and about 10 km high, were recognized for the first time from the Mariner 9 photographs. There is also evidence of many smaller volcanic features scattered over the surface of Mars.

The presence of volcanic activity on Mars does not in itself imply polar wandering but, as Murray and Malin point out, it is instructive to determine whether or not the extrusion of such a large mass of material could have pro-

Frameshift Suppressor Transfer RNA

FRAMESHIFT mutations arise from the insertion or deletion of a nucleotide, or any number of nucleotides other than three or multiples of three, into a gene with the result that the reading frame of all triplet codons distal to the mutation is changed. Such mutations can be internally suppressed if a compensatory mutation occurs in the same gene. For example, a frameshift mutation resulting from the insertion of a base is suppressed by the deletion of a neighbouring subsequent base. Frameshift mutations can also, however, be suppressed if a transfer RNA molecule is mutated so that it can read non-triplet codons in which case suppression is said to be external. Several external suppressor mutations of frameshift mutations of the histidine operon of *Salmonella typhimurium* have been isolated and one of these external suppressor mutations, the *sufD* mutation, has now been characterized by Riddle and Carbon.

In *Nature New Biology* next Wednesday

(April 18) they describe an elegant set of experiments which establish that the *sufD* mutation is located in a structural gene for a species of glycine tRNA which reads the codon GGG. Their experiments also prove that the tRNA molecules specified by *sufD* mutants have an anticodon sequence CCCC instead of the anticodon sequence CCC present in the wild type tRNA. This tRNA might therefore translate frameshift mutations which involve the change of a GGG codon to a GGGG quadruplet or the additional base in the tRNA anticodon may "simply serve as a spacer, so that the tRNA occupies an unusually large space over the message and so suppresses +1 frameshifts". But whatever the mechanism, the striking fact Riddle and Carbon have found is that certain frameshift mutations resulting from the addition of a single base are suppressed by a species of tRNA carrying an additional base in its anticodon.

duced a rigid body nutation. In fact, calculations show that the Nix Olympica mass, for example, is likely to give a rigid body nutation of only 0.04° . Thus even the effect of the four largest shield areas will be at least two orders of magnitude smaller than the polar wandering implied by the quasi-circular polar features. But is Mars a totally rigid planet? The fact that the observed value of the primary coefficient of the low order harmonics of the Martian gravity field is close to that expected from a rotating planet in hydrostatic equilibrium suggests that, although Mars has a rigid surface, its interior may be hot enough to support viscous motion. In this case, the nutation could be much higher than that predicted on the basis of a rigid body. Moreover, the presence of viscous motion itself implies mass movements much greater than those represented solely by the exposed shields. The existence of what amounts to mantle convection would be consistent with polar wandering but, as in the case of the Earth, would not be sufficient to prove it.

A third feature of Mars relevant to the polar wandering argument is that the low degree spherical harmonic coefficients (non-hydrostatic) of the gravity field are relatively larger than those of the Earth. On Mars they also correlate significantly with surface topography and geology, whereas they do not do so on Earth. Thus, for example, the apex of the equatorial bulge for both the gravity field and the planetary surface correlate well with the location of the four large shield volcanoes. This phenomenon could be taken to support the connexion between large-scale volcanism and deep-seated density differences which would be expected at the start of large-scale mantle convection, although, perhaps unfortunately, an interpretation could also be made in terms of a totally rigid Mars. To this extent, the gravity data are equivocal.

Nevertheless, at least three different aspects of Mars are at least consistent with polar wandering. But if polar wandering has taken place, or is taking place, what is its rate? The equatorial shield areas contain few impact craters, and so they are probably no older than a few hundred million years. This gives a rough idea of the time scale involved. The polar features may, however, give a more accurate result. Assuming, as Leighton and Murray (*Science*, **153**, 136; 1966) did, that each lamella of the laminated terrain represents a 50,000-year climatic period, the clearly distinguishable polar plates may represent about 5×10^7 yr, and the more eroded plates offset from the present axis by up to 20° may represent about 10^8 yr. On this basis, the polar wandering rate would be about 5×10^{-9} rad yr $^{-1}$ or about 20 arc min per million years.

NUCLEAR STRUCTURE

Testing New Models

from a Correspondent

THE study of nuclear physics has long since fissioned into nuclear structure and high energy physics, a division which is formally recognized in conferences such as that held in Liverpool from March 28 to 30 under the auspices of the Institute of Physics. (In turn there has appeared to be subdivision within nuclear structure physics too, but the boundaries seem less clear.)

At the Liverpool conference Dr R. Chapman (University of Manchester) surveyed the evidence for a dramatic departure from the rotational model sequence of energy levels which occurs at high angular momentum in heavy nuclei. This phenomenon is now ascribed to a phase change in the nucleon motion from that of a superfluid to that of a near rigid rotor. Thus from failures of simple models much is learnt about the physics of the nucleus. The same general point was mentioned by Dr R. R. Whitehead (University of Glasgow) in the very different context of large-basis shell model calculations for light nuclei. By ingenious computational techniques and the use of large

computers it is now possible to make traditional shell model calculations for nuclei in the 2s-1d shell without resorting to the usual pruning of smaller wavefunction components. Dr Whitehead argued that whereas it was possible to contrive agreement between model and experiment by using effective nuclear forces to cover up for a truncated calculation, a better idea of the real nuclear forces would be learnt from the success or failure of the fuller calculations.

Although recognizing the importance of these mammoth calculations, many physicists—and especially experimenters—feel the need for a complementary simple model whereby they may grasp some meaning from the various data over a range of nuclei. Dr P. W. M. Glaudemans (University of Utrecht) described such a model for s-d shell nuclei using the so-called surface-delta interaction. Although this schematic model is nominally of the shell model type, the effective interaction used enables it to reproduce some of the observed strong electromagnetic transition strengths which betray the presence of collective nuclear motion.

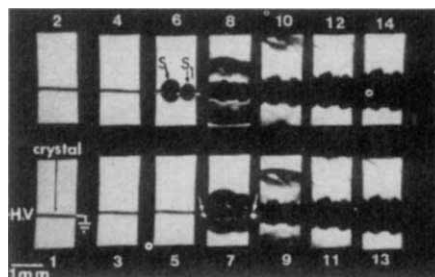
The experimental evidence for such collective motion in s-d shell nuclei has grown rapidly in the past few years.

Explaining Electric Detonation of Explosives

ALTHOUGH it is well known that solid explosives can be detonated by electric fields and electric discharges, it is not clear just what mechanisms are at play in the process. Some have suggested that, in the case of azides like $\text{Cu}(\text{N}_3)_2$, the explosion can be traced back to a breakdown of electrical resistance caused by the injection of holes from the anode or of electrons from the cathode. Another question that arises is whether mechanical shock or thermal shock arising from the electrical breakdown is responsible for the triggering of the explosion.

In next Monday's *Nature Physical Science* (April 16) Chaudhri describes a study by means of high speed photography of the early stages of this kind of detonation. The figure shows a sequence of photographs taken at a rate of 5 million frames a second of the stages in the decomposition of a single crystal of silver azide (AgN_3). A negative pulse of amplitude 10 kV and rise time about $0.5 \mu\text{s}$ was applied between frames 2 and 3, and it reached a maximum between frames 4 and 6. Two dark expanding regions S and S₁ are in evidence in frame 6, and, significantly, they are well away from the electrodes. The later frames suggest that the dark regions arose from shock waves. Chaudhri says, however, that it is not clear whether the shock waves he observed are the

result of electrical breakdown or the initiation of fast decomposition at these points.



The electrical initiation of a reaction in a crystal of AgN_3 . The electrodes are steel plates. The single crystal is $\sim 100 \mu\text{m}$ in diameter, and the whole arrangement is situated in a container filled with oil.

Another sequence of photographs, this time taken at a rate of 10 million frames a second, reveals an initial dark spot in the crystal near, but not at, the anode. It would seem that the propagation speed of the reaction was some $1,750 \text{ m s}^{-1}$, about 70 per cent greater than the normal propagation speed. Chaudhri concludes that the reaction does not start because of impact ionization and decomposition by electrons injected from the cathode, but he says that more work will have to be done to pin the mechanism down.

Some pattern is emerging from the welter of data obtained, chiefly as a result of improved detection, electronics and on-line computing facilities. Dr P. J. Twin (University of Liverpool) showed examples of the combined power of the measurement of lifetimes, X-ray angular distributions and polarizations in elucidating the level schemes of these nuclei. The broad overview is that the nuclei around Mg are deformed and prolate with a change to oblate shape at around ^{28}Si . So the systematics here reveal shape transition, a phenomenon which has motivated much work previously on heavy nuclei.

Dr P. G. Hansen (University of Aarhus and CERN) described some sophisticated experiments at CERN on nuclei well off the stability line. For example the isotope effect has been measured for several neutron-deficient mercury isotopes. This seems to follow the simple dependence on neutron number of a straightforward volume effect down to ^{185}Hg where there is a distinct break. A sudden onset of nuclear deformation might explain this but it has not been confirmed by independent evidence. The Scandinavian workers have been speculating on the existence of the bubble nucleus. This would be spherical but would have a small hollow centre and it would favour high angular momentum states.

Professor J. de Boer (University of Munich) gave a handyman's guide to the principal features and parameters of heavy ion Coulomb excitation. This process affords direct measurement of nuclear electric multipole matrix elements. Current interest is in the measurement of static quadrupole and transition hexadecapole moments which are tell-tale signs of the nuclear charge distribution.

By virtue of parallel sessions it was possible for anybody to contribute. There was also time to hear Professor H. Fröhlich (University of Liverpool) and Dr N. MacDonald (Glasgow) elevating biology by bringing to that field—with humour and effect—some methods of theoretical physics.

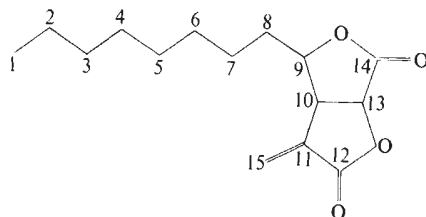
NMR

^{13}C and Avenaciolide

from our Chemical Physics Correspondent

FOR many years isotopic labelling with radioactive ^{14}C has been widely used in biosynthetic studies and it is not immediately obvious why anybody should prefer to use the stable isotope ^{13}C . Yet this is precisely what Tanabe, Hamasaki, Suzuki and Johnson (*J. Chem. Soc. Chem. Commun.*, 212; 1973) have now done in their study of avenaciolide (see diagram). In its biosynthesis by the metabolite

Aspergillus avenaceus they have used in the feedstock $^{13}\text{CH}_3\text{COONa}$ and, separately, $\text{CH}_3^{13}\text{COONa}$, and have confirmed that the C_8 side chain and principal skeleton have the expected alternating origin for the carbon atoms; 1,3,5,7,9, and 13 are derived from the CH_3 groups and 2,4,6,8,10, and 14 from the $-\text{COO}-$ groups. They have also confirmed that the adjacent atoms 11 and 15 may both come from the CH_3 sites as would be expected if they were derived from the central atoms of a succinic acid intermediate.



Structure of avenaciolide.

The ^{13}C atoms in the product are, nowadays, readily detected with a Fourier transform NMR spectrometer with proton decoupling facilities. This technique greatly improves the signal-to-noise ratio of the record, first because signals are detected from all the ^{13}C nuclei throughout the measuring time instead of the resonances being recorded separately one after the other; the information is then unscrambled and presented in regular spectral form by a computer. Second, the improvement arises from the

collapse of a multiplicity of peaks into a single line of the same total strength, which occurs because all the influence of the carbon-proton spin-spin coupling is removed from the spectrum. Although the sensitivity is even then poorer than that of radioactive tracer work with ^{14}C , it is quite sufficient provided that the biosynthetic growth process does not involve appreciable dilution of the feed material.

When the ^{13}C technique is applicable it has several established or potential advantages. First, all labelled positions can be identified from the chemical shifts without the need for any chemical operations comparable to the selective degradations required to establish the site of ^{14}C . Second, in principle the enrichment of each site can be determined from the signal strength. Third, the technique is non-destructive and so the product is available for further use. Fourth, for substitution at adjacent sites the carbon-carbon spin-spin coupling can be used to identify such double labelling. In other words, the technique can distinguish a mixture of the type $^{12}\text{C}_a-^{12}\text{C}_b$ and $^{13}\text{C}_a-^{13}\text{C}_b$ from a mixture of the types $^{13}\text{C}_a-^{12}\text{C}_b$ and $^{12}\text{C}_a-^{13}\text{C}_b$ and indeed could detect and quantify a mixture of the last three species. Fifth, in multiple labelling experiments it could distinguish $^{13}\text{C}-\text{D}$ from $^{13}\text{C}-\text{H}$ and also $^{13}\text{C}-^{15}\text{N}$ from $^{13}\text{C}-^{14}\text{N}$ groupings. With these attractive features it will be surprising if ^{13}C labelling is not exploited to a great extent in future biosynthetic experiments.

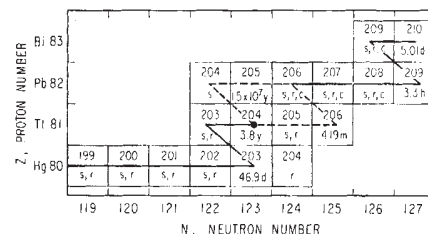
Stellar Nucleosynthesis and the s-Process

THE importance of the short-lived s-process chronometer ^{205}Pb , its relation to the mechanism of s-process nucleosynthesis and its implications for cosmochronology are discussed by Blake, Lee and Schramm in next Monday's *Nature Physical Science* (April 16). So far, the only reliable indicators of nucleosynthesis timescales are for the r-process, which proceeds rapidly by neutron capture and yields, ultimately, very heavy elements such as ^{235}U and ^{238}U . The s-process, of course, also proceeds by neutron capture, but slowly by comparison with the associated β -decay process, chiefly involving light elements initially and building up to, for example, Sr, Zr and Pb.

The importance of finding an s-process "chronometer" lies in the estimate it would provide of the time between the solidification of Solar System material and the end of the sequence of events which produced the element abundances observed in the Solar System.

One of the important links in the chain of element building occurs in the lead-thallium region (see diagram).

Here, there is a possible branching of the s-process at ^{204}Tl ; this is shown by dashed lines in the figure, where r denotes r-process, s denotes s-process, and c indicates cosmogenic origin.



The most probable s-process site is in the interior of red giants. According to Blake *et al.*, the time scale for the s-process is comparable with that derived from the r-process, so that all Solar System material from all nucleosynthetic sources separated over the same time, between 0.7 and 1.1×10^8 yr according to present estimates. With better measurements, this should provide an insight into the processes involved in the formation of the Solar System.

Uncertainties in Energy Policy

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This article describes the factors that affect the way in which Britain's fuel needs are met.

Two sets of problems are posed by the present energy situation. The first is concerned with the supply fuels of all kinds available to meet British requirements and their relative cost. The second group relates the British situation to conditions in the European Community, the United States and the world generally. Any discussion of any energy policy for Britain must take place within the perspective of the world situation both as regards price elasticities in particular markets, and more broadly in relation to global resources and their pattern and rate of use. As Britain begins to familiarize itself with the implications of the new political imperatives of Community policy harmonization and coordination, the questions to be answered in formulating a British energy policy inevitably involve external factors and their impact on national policy making.

Policy Ingredients

The ingredients of a British energy policy are a mixture of indigenous and imported fossil fuels together with a relatively small quantity of nuclear energy, the balance of payments cost of the former and the opportunity costs of the latter. The proportions in which they are put together, the methods by which they are produced, and the degree of choice open to the consumer, have varied according to political and economic pressures over the years. The common factor has been the continuing tendency for the demand for electricity to double every ten or eleven years, and that for petroleum for motor transport to rise by 5 per cent a year. If this rate of increase is extrapolated transport will have moved up to take 30 per cent of total energy in the year 2000, compared with 15 per cent today. Up to now the market has been left to vary the proportion of the increasing total needed to be met by coal or oil, with nuclear energy in a long-stop position turning out some 9 per cent of the total electricity generated.

On the supply side the dominant factor has been the relative cost of coal and oil, with coal losing out to the readily available supplies of cheap oil which appeared on the market as a result of the discovery and development of new reserves in the Middle East and Africa from the middle 1950s onwards. One result of making cheapness one of the chief policy priorities has been increased dependence on imported fuel. In 1955 imports accounted for only 14 per cent of British energy consumption, by 1970 the figure was 45 per cent. In the EEC during the same period the proportion of imports rose from 20 per cent to 63 per cent. Figures of this kind must of course be related to use. The rise in the number of motor vehicles on British roads accounted for a considerable part of the increase. At the same time it would have been less than sagacious to burden industry with high fuel costs by too stringent limitations on the use of oil. A rationalization of the coal industries of Britain and the Six was an essential stage in their post-war economic development. The way in which it was carried out, however, ignored the special problems of the fuel industries. Decisions to switch over from

coal to oil-burning power stations have to be related to the availability and price of fuel over the lifetime of the equipment. This is likely to be of the order of 25 to 30 yr for coal or oil burning plants and 25 yr for a nuclear plant. An appreciable increase in the price of fuel during this period can only be adjusted to at a considerable capital cost. The four-fuel policy (coal, oil, natural gas and nuclear energy) introduced in the White Paper¹ of 1967 has since been overtaken by the discovery of North Sea oil, the advance in the price of imported oil as a result of the activities of the Organization of Petroleum Exporting Countries (OPEC), and the dramatic changes in the international energy situation which have led to an increasing dependence on imported fuel in the United States. British membership of the European Community has introduced a further set of uncertainties into the situation.

The Rome Treaty did not bind the Six to the introduction of a common energy policy, and responsibility for energy matters was divided between the EEC (oil), the European Coal and Steel Community (coal), and Euratom (nuclear energy). Various initiatives, notably those of 1964 and 1968, have been taken by the Commission towards the formulation of a common energy policy, none of which have gone beyond an appreciation of the situation, and the circulation of information and statistics. The emergence of a situation in which the enlarged Community is dependent for 60 per cent of its energy requirements on imported oil has concentrated attention on the need for a common energy policy which would ensure a better utilization of the indigenous fuels of the Community and a more rapid development of nuclear energy supplies. Another aspect of the situation is the demand that the nine should negotiate as one with OPEC and other sup-

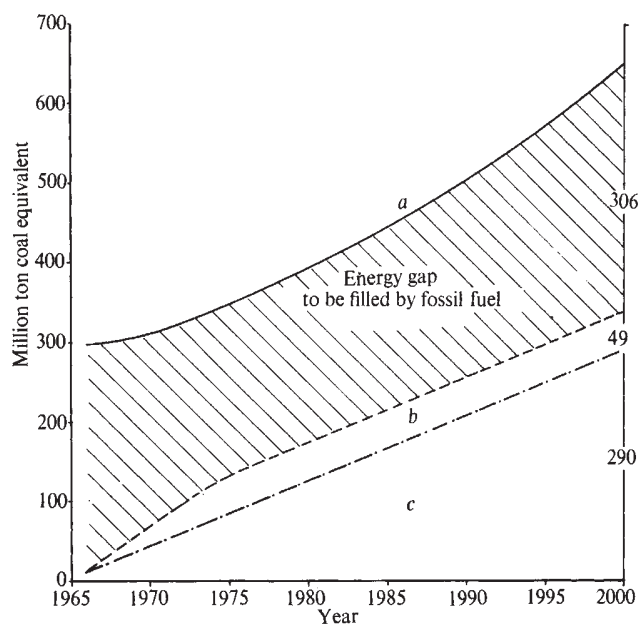


Fig. 1 Projections showing the total fossil fuel energy gap up to the year 2000 for Britain. For 1966 the energy requirement was 297.7 million ton coal equivalent (coal, 174.7; oil, 111.7; nuclear, 10.2; natural gas, 1.1), a, Total energy; b, natural gas; c, nuclear energy. From OECD energy statistics.

pliers of imported fuel. For Britain a Community energy policy poses a number of questions. On the credit side, Community membership opens up the possibility of increased British exports of coal to the rest of the Community. Coal production in the Nine totals some 300 million ton, about a quarter of Community energy requirements. Britain, with an output of some 140 million ton in a normal year, will be able to export increased tonnages to the Continent working up to an estimated 10 million ton.

The prospect of increased sales to other parts of the Community could improve the financial position of the National Coal Board (NCB) by spreading costs over a larger tonnage, and would also reduce its dependence on its principal customer, the electricity supply industry. At the same time the coal industry must now put its research and development programmes into top gear. In the long years during which it began to look as though the only good coal mine was a closed one, there was little incentive to press forward with research into methods of increasing the calorific efficiency of coal.

Today the NCB is able to turn its attention to research and development in both the coal winning and coal utilization fields. The rediscovery of the importance of coal has brought changes in the orientation of this activity. Increasingly research and development programmes in coal are being linked up with those of upstream and downstream interests. This means that machinery manufacturers and users, transport agencies and environmentalists are all interested in new ways of producing and using coal. What is lacking at present is a steady input of information on research and development on other fuels. When this happens and attention is being given to energy resources rather than to individual fuels there will be some hope of securing a coherent energy policy. So far no minister has been in a position to introduce a common research and development policy for energy as a whole, not only in Britain but on a Community-wide basis. Perhaps the increasing urgency of the situation will bring home the fact that competition does not increase the total quantity of finite resources but only their availability.

Each of the fuel industries, meanwhile, is pressing forward with its own research and development programmes. The NCB, for example, has many long and short-term projects designed to fit a situation which calls for increased efficiency in use coupled with reduced pollution. The sort of things that are under investigation are ways and means of increasing the power and reliability of coal-cutting machinery and the introduction of machinery for the automatic sensing of coal seams, able to distinguish between rock and coal. Other areas being studied are the development of smokeless fuel, smoke-eater appliances, and the utilization of colliery shale for structural and other purposes.

The change in the world energy situation which makes urgent policy decisions necessary is the extraordinary growth in demand for energy of all kinds in the past two decades. World energy consumption trebled between 1900 and 1950, a period which took in two world wars, the development of the aircraft industry, and the proliferation of motor transport. Since 1950 world energy consumption has trebled again and the situation now is that world requirements are growing at the rate of 300 million ton of coal equivalent every year. If this rate of increase continues, let alone increases, the possibilities of meeting requirements from fossil fuels are, to say the least, problematical. Gloomy prophecies of coming shortages can be borne with fortitude when it can be assumed that their chief impact will be on other people. The distinctive feature of the present energy situation is that it is making itself felt already in the United States, the world's greatest consumer of energy, where aircraft have been reported to be having difficulty in refuelling at Kennedy Airport.

The causes of the United States crisis are already well known². The significant fact is that the United States will from now on be increasingly dependent on imported energy

and has indeed removed import restrictions on imported oil. In 1970 imports supplied 12% of the energy requirements of the United States, by 1984 they will have increased to at least 30% on present trends. In any discussion of this kind it is all too easy to fly away on a science fiction broomstick and forget that energy demand has to be considered in terms of prices as well as predictions of quantities. Higher prices for Middle East oil not only encourage exploration and development in other areas, but give a new urgency to research into new forms of energy. On the political front the need to bring undeveloped resources into use results in unexpected policy realignments of which the most dramatic so far is the United States/Soviet Union trade agreement of October 18, 1972, which provides among other things for cooperation in exploiting the natural gas resources of Siberia for the benefit of the American fuel economy.

In terms of world energy production oil now supplies nearly half the total (3,050 million ton c.e.) followed by coal (2,500 million ton c.e.) and natural gas (1,300 million ton c.e.). Nuclear energy in 1970, the year to which the above figures refer, provided only 200 million ton c.e. The industrialized countries with the United States at their head, who are responsible for this increase, have only been able to maintain consumption by greatly increasing their imports over a relatively short period. Japan whose energy requirements have risen from 50 million ton c.e. in 1950 to 410 million ton c.e. in 1970, with the expectation that this will double by 1980, has now reached a point where 90 per cent of its fuel requirements are imported.

This upsurge of fuel imports into the industrialized countries has been made up almost entirely of oil from the Middle East and Africa. As far as can be gauged from statements about proved oil reserves this situation, in which one group of countries produce more and more oil to meet ever increasing demand from a totally different group, seems likely to continue. In market terms the members of OPEC are in a position where their long-term interests will be best served by higher revenue per barrel rather than by an increased volume of sales. Libya and Kuwait have already moved in this direction and it seems likely that Saudi Arabia and Iran may decide to conserve supplies also. The host governments' "take" rose by about 50% a barrel as a result of the agreements negotiated with OPEC in 1970 and 1971. It remains to be seen whether these will provide a basis of price stability or whether further substantial increases lie just ahead. A further aspect of the oil supply position is the high cost of production elsewhere in such relatively difficult areas as the North Sea and Alaska. The importance of the North Sea discoveries should not be underestimated, but with production of about 4 million barrels a day in the 1980s it will only be providing about a sixth of the estimated requirements of the Community at that time.

Natural gas provides about a quarter of the energy needs of the industrialized countries. Here again the position is aggravated by shortages in the United States, where reserves are now way below their 1964 level. The importation of liquefied natural gas, particularly into the eastern states will become increasingly necessary. World reserves of natural gas are significantly less than those of oil, and shipments of liquefied gas are only economically feasible at high prices. Release from the world energy dilemma will not come from natural gas, but the geographical distribution of reserves gives an advantage to Britain and other Community countries for the next decade, provided it is not used for purposes for which it is not basically suitable.

After its decline during the cheap energy decade coal is now recognized as having an essential part to play in making up total energy requirements. As one of the world's most plentiful natural resources it could continue to meet its present consumption levels for an estimated 2,000 yr+. Even with consumption increasing at 2% a year reserves would last for 200 yr. There is therefore a secure place for coal in

the energy budgets of the industrialized countries. In Britain this need has been given *de facto* recognition by the government's decision to make grants up to £720 million to the industry over the next five years, and to cancel some £475 million of the NCB's debts. The important feature of this package is not its size but the fact that it acknowledges that market forces by themselves will not produce the required fuel supplies in the right amounts. The grants for particular regions, which amount to £210 million, are not a welfare gesture to keep unprofitable pits going in villages dependent on them for a livelihood, but a means of ensuring that their production will still be available in two or three years on the assumption that oil prices will go on rising.

From what has been said of the fossil fuels it is clear that although a world fuel crisis is likely it is not inevitable. The era of cheap energy in apparently inexhaustible quantities is over. During the 1970s we shall be moving towards a new situation with higher fuel prices acting to keep up the level of supplies, and with increased research activity bringing improvements in the utilization of existing fuels and the discovery of new energy sources. At the same time constraints will be introduced from other motives, for example the opposition by the environmentalists to strip mining at one end of the scale and to the proliferation of nuclear plants at the other. The changing pattern of activity within the energy industries will no doubt produce supplies sufficient to meet the demands of the industrialized countries, at a price. The question is what this price will be not simply in money terms but in social and environmental terms. While the fossil fuels, the world's capital, are being run down, efforts to realize new energy forms, notably solar energy and nuclear fusion, will continue.

As far as Britain is concerned the fact that there is no Community energy policy is an advantage. Britain, with the largest coal production and the as yet unquantified re-

sources of gas and oil in the North Sea, should have a considerable say in future policy initiatives. But this will not be without its problems. One of these is the question of price standardization, which in the case of gas gives a price 30% lower in Lille than at Dusseldorf for gas from Groningen. A related problem is that of the taxation of fuel which varies according to national priorities from one Community country to another. Leaving aside these problems of commercial and fiscal harmonization certain principles for a Community energy policy emerge. The first is that a high priority should be given to security of supplies which means ensuring the maximum use of indigenous fuels. This raises the question of what priority to give to North Sea oil and gas compared with coal and imported oil. The common sense answer would seem to be to use North Sea oil primarily to replace imported oil rather than substituting it for coal in power stations. North Sea gas should not be used extravagantly but conserved by concentrating on premium uses. Nuclear power should be regarded as the long-term takeover fuel and every effort should be made to reduce the capital cost of nuclear power stations and their running costs in order to enhance the competitive position of nuclear electricity. The policy of supporting coal which has been introduced by the British government should continue. In the background but with increasing importance to the solution of the energy problem is the question of research and development. This will clearly have to move on to a Community from a national basis. More importantly it should be concerned with energy requirements as a whole, not with individual fuels. The opening of energy research stations in the Community would be a welcome indication that the scale and significance of the energy problem had at last been recognized.

¹ Cmnd 3438 (HMSO, 1977).

² *Nature*, **240**, 249 (1972).

Can Design be Taught?

PETER EVANS

Department of Metallurgy, University of Manchester Institute of Science and Technology

Dr Evans examines to what extent "design technology" is a meaningful concept.

I SHALL start by postulating a relationship, namely that design is determined by function and technology. That is, it is determined by what the "machine" has to do and how good a machine can be made in the present state of technology. I use "machine" in its widest sense so that it includes teacups, shovels, baths, computers, kitchens, motor cars, hospitals, houses, roads, cities, and so on. A limitation is set by the materials used to make the machine because the properties of the materials will not only place bounds on the final use to which the machine can be put (for example the temperature it can be used at, or whether it is waterproof or resists corrosion) but will also determine how they can be manipulated in the course of making the machine; they will therefore limit the possible forms the machine can take. The major limitation, however, is

more likely to arise because of an inadequate understanding or definition of the function of the machine or because the user has not decided (where he is free to do so) on the relative importance of the many functions, or has simply not recognized the relative importance of the many functions.

Design is determined by function and technology. So we can make glass houses. But it has to be remembered that people throw stones and, however much the glass is improved, people are not, on that account, going to stop throwing stones. In other words the human element must be taken into account when interpreting the function of the machine, that is, simple mechanistic terms are inadequate.

It is important to maintain a fresh approach here, in particular over the concept of function. Thus the prime function of a machine can be defined, and then any subsidiary functions and the order of precedence of the many-functioned machine. Having done this, one can go on to formulate means of fulfilling this function (but see later) and, inevitably, arrive at a compromise solution. After doing one's own thinking on the problem one can at this stage, but not before, examine any previous solutions that exist and decide how well they fulfil the principal and subsidiary functions of the machine. Any advances in techno-

logy since the realization of these earlier designs (that is, solutions) can then be considered and a more efficient and/or elegant solution produced. I stress the importance of doing one's own thinking when first confronted with a problem (the analysis of function, in the example quoted above) for, if one starts by examining other solutions, one's thinking is inevitably affected by the approach used in the earlier work. It is only by doing one's initial thinking *in vacuo*, as it were, that one can hope to produce new concepts. (There is sound support for this viewpoint from that prolific inventor Sir Henry Bessemer.)

How then can "design" be defined? In general terms I would use "design" as the opposite of "chance" (it has some connotation of imposing order and therefore, in statistical thermodynamic terms, a low entropy state). In the more specific terms of the present context I would define design as the solution to the problem of how to fulfil a recognized function within the limits of our technology. This presupposes, of course, that the elemental function or functions of the proposed machine have been recognized. The ways of doing this will vary somewhat from an individual's solitary "communing with nature on the mountain" to a "brain storming" session by a team.

In recognizing the function or functions of the machine, one enters the realm of analysis. When one comes to formulate a solution one must invoke synthesis. Analysis is essentially a resolving, into component parts of a problem, an idea, or a thing. Synthesis is a "making a whole out of parts". There is, when the two concepts, analysis and synthesis, are set side by side in this fashion a great difference. It is well known, in a general way, that creating is more difficult than destroying, putting together more difficult than taking apart, but I want to propose a semi-quantitative assessment that has not, I think, been suggested before. It is simply this: suppose one can analyse something into six components parts—we have started with an entity, a given thing, and produced six parts. But suppose one starts with six parts, then in general they can be put together in different ways and if the order in which they are assembled is significant then in the limit there are $6!$ ($=720$) ways of putting these six parts together. If only one sequence is significant then the chances of hitting on it are smaller than the chances of discerning six parts in a given whole—there is, in fact, a gulf between analysis and synthesis. Whereas analysis has been taught for years under the guise of "the scientific method", the question here is can synthesis be taught? As we must relate our activity to people (it becomes meaningless if we do not) we might start by taking some feasible pattern of life as a base line on which to build, but this is a stifling approach: one must not seek to impose a pattern on humanity. The infinite variety that makes up human activity is to be accepted with gratitude and if people cannot be taught how to design beauty into their machines, as there is no agreement about what constitutes beauty, then they can be taught to design efficiency, comfort (or ease of operation), and safety into the machine. One might hope to add a sense of variety as opposed to undiluted functionalism.

In what ways might one go about this, what are some of the disciplines to be drawn on, and in what new directions should one be looking? The field of ergonomics should be culled (but beware the jargon that sometimes creeps in). The applied psychologists should be consulted and asked to say what they mean in plain English and more experiments should be carried out in this field. A great deal of attention should be paid to spatial relationships, in particular the void must be regarded both as a divisor or separator between solid masses and as a "negative solid". We should consider motif, repetition, pattern, growth and form and the mechanics of growth and form, for example, shells, the different shapes of fish, the thickening of tree branches where they join the main trunk where the bending moment

has its greatest value, and so on.

Virtually all machines (paper weights and door stops possibly excepted, although even they have to be moved into place at least once) have a dynamic aspect and the study of this would be of great importance. It should not be confined to the relative movement of man and machine or fluid and machine, but the flow of people themselves (for example at railway stations, in offices, along paths between campus buildings) or the flow of traffic at different places and at different times and the people/traffic interaction. One should recognize and measure both instantaneous flow patterns and the changing flow pattern over a period (some concepts from solid state physics may be useful here). One must study (or enlarge the studies of) what might be called "proximity effects", that is, how close people can stand other people with whom they only relate in an "average" way (this could be considered an extension of what used to be called by the sociologists "small group dynamics"). One can envisage circumstances where the presence of other people would be reassuring and improve the performance of a task, and circumstances where other people were so close as to irritate and hinder performance. Such studies would have particular relevance in determining the size and layout of buildings in relation to their function.

From here I shall consider size in general. As much of design is by its very nature concerned with the future, attempts must be made to forecast future trends in diverse fields such as population growth, the siting of industry and of new towns, and to identify desirable and likely developments in technology. Here we must not fall into the trap of making an extrapolation (be it linear or exponential) from recent trends. It is indeed essential to reconsider some of the *idées reçues* on such things as optimum size, and it is to be hoped that the notion that bigger does not necessarily mean better will gain more acceptance. In terms of population growth there is a factor that has been overlooked, but which is very relevant in the present context. To explain it I shall borrow a concept from nuclear physics. This is the concept of "cross-section". Roughly stated, this says that if a particle is moving it takes up more room than if it stays still, that is, it has a larger "cross-section". Now the same can be said of people. A million people in the mid-twentieth century effectively take up more room (and use more natural resources, produce more waste, and so on) than when people were less mobile. Also, continuing to borrow from nuclear physics, the probability of collision increases with increasing cross-section, that is, in terms of people the probability, not so much of physical collision, but of tension and a sense of physical oppression increases with increased cross-section as this adds to the sense of crowding for a given population. Thus, while increased mobility brings greater "freedom" in one sense, it also brings more interaction, thus reducing freedom.

Finally, I shall mention some other areas of interest (the list is by no means exhaustive): the concept of fashion in the use of materials and the "hangover factor", whereby features arising simply from the nature of one material are deliberately copied when a different material is used, for example wood-grained 'Formica' (this can become a legitimate element of pattern or texture); the problem of defining scales for design assessment—is this meaningful?; lessons to be learned by examining national solutions to design, that is, are there any other influences at work besides different life styles, climates, and local materials?; properties of materials dictate manufacturing techniques and limit design (but "art triumphs over its medium"); the use of film in teaching (anything), how effective is it?; form and function, fitness for function, "fun" and function, that is, the inclusion of the apparently irrelevant which has a great effect on the real as opposed to apparent efficiency of the man/machine system—a big potential field for research, and a suitable note on which to end this summary.

Seismic Travel Time Evidence for Lateral Inhomogeneity in the Deep Mantle

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We present evidence from seismic travel time data of lateral variations in the properties of the lower mantle. The size of some anomalies is about 1,000 km.

EVIDENCE from seismic body wave and surface wave data has long indicated that the Earth's upper mantle (depth < 700 km) is strongly laterally heterogeneous. Lateral variations of the compressional wave velocity as large as 10% have been reported for the upper 200 km, and the shear velocity probably varies even more. For depths greater than 700 km, however, the existence of lateral variations has been more difficult to establish, although such variations have been invoked by various workers^{1,2} to explain the scatter of some seismological data. Greenfield and Sheppard³, in a study of $dT/d\Delta$ measurements made at the Large Aperture Seismic Array in Montana, found a pronounced difference between data from events to the northwest and the southeast for epicentral distances greater than 60°, which could not be attributed to the structure beneath the array, and seems explicable only in terms of heterogeneities in the lower mantle. Davies and Sheppard⁴ have presented a more extensive collection of data of this type in the form of an "array diagram", on which $dT/d\Delta$ and azimuth anomalies are represented as vectors in slowness space. Many anomalies are found which are too large to be effects of upper mantle heterogeneities in the source regions; on the other hand, the anomalies often vary rapidly with the direction of approach of the waves, implying that structure directly beneath the array is not responsible. Further evidence has come from a study of the diffraction of compressional waves by the Earth's core, in which Alexander and Phinney⁵ found that the region of the core-mantle boundary beneath the Pacific Basin is distinctly different from the region beneath the North Atlantic and Africa.

Travel Time Anomalies

We have found evidence that significant lateral variations occur in the lowest few hundred km of the mantle, this region being much more heterogeneous than that which lies above it. The methods of this travel time study are described in detail elsewhere⁶.

We restricted the study to data from deep focus earthquakes in an attempt to avoid systematic errors caused by near source velocity variations in the upper mantle, which are particularly severe in seismically active regions. About 3,300 arrival time data from 47 earthquakes with depths between 450 and 650 km were used, all events being located in the deepest parts of their

respective seismic zones. For most of the 18 seismic regions involved, two or more events were available, and for each station a consistency check was made to eliminate data contaminated by gross errors. An iterative procedure, similar to the one described by Herrin *et al.*⁷, was then used to determine the earthquake locations, the travel time curve for a 550 km focal depth, and a set of "station corrections" (each represented by a constant) to account for the effect of lateral variations in the upper mantle beneath the stations.

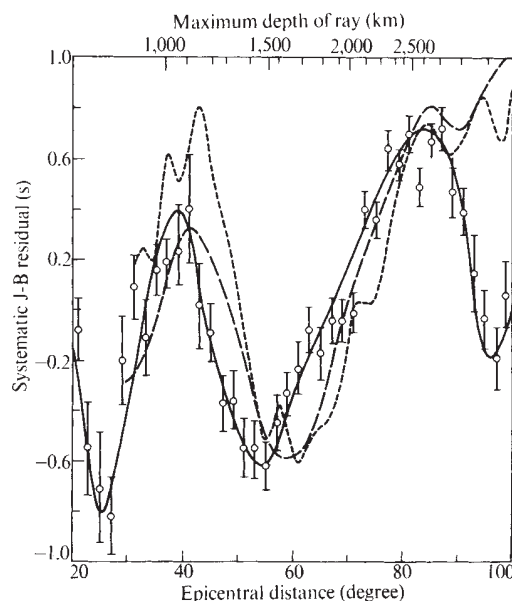


Fig. 1 P wave travel time curve (focal depth 550 km) determined in this study (—), expressed in terms of deviations from the Jeffreys-Bullen values. Data means and their standard errors are indicated for 2° distance intervals. Surface focus curves of Herrin *et al.*⁷ (—) and Lilwal and Douglas⁸ (---) have been displaced vertically for ease of comparison.

The travel time curve thus determined is shown in Fig. 1 (in terms of deviation from the standard Jeffreys-Bullen tables), together with the data means and their standard errors for 2° distance intervals. This curve is similar in shape to those found in other recent studies^{7,8} except beyond 85°, where most other curves remain approximately parallel to the Jeffreys-Bullen curve, but ours becomes progressively earlier by about 0.9 s. Fig. 2 shows some of the data which have contributed to the determination of the travel time curve; the observed times show a striking dependence upon the location of the earth-

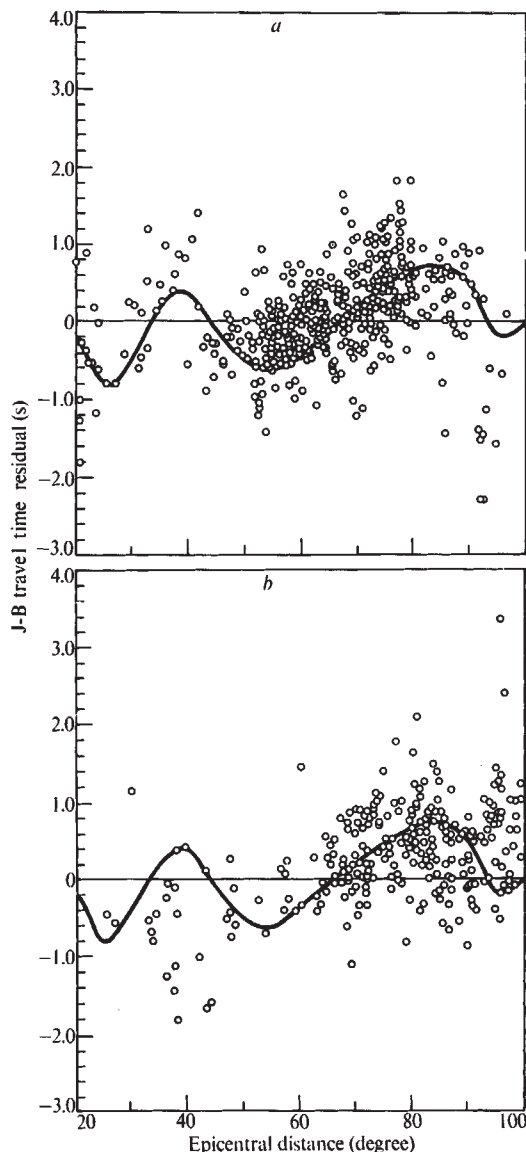


Fig. 2 Travel time data (with station corrections applied) for earthquakes in (a) the Sea of Okhotsk and (b) Argentina. The solid line is the curve derived from all data.

quakes. The difference between the curves in Fig. 1 results from differences in the geographic regions sampled. Possible causes of a regional dependence of this nature are velocity variations in the upper mantle in the source or receiver regions or in the lower mantle, and mislocation of the events (caused by uneven station distribution, and so on). Event mislocation and structure in the receiver regions can be ruled out because they would be expected to produce similar effects at all epicentral distances. Although the observed variations are most striking beyond 85° , we shall show that they are much smaller at distances less than 70° . It is conceivable that structure in the source regions could produce a distance dependent regional variation of this kind, if the velocity anomalies were systematically located relative to the earthquake hypocentres (as indeed they are beneath island arcs). In that case the variations would have to be localized in a very small region beneath the hypocentres, because a 10° distance interval maps into about a 5° difference in angle at the focus. Even if the anomalous regions are as deep as 1,000 km, the velocity change must occur over a horizontal distance of only 50 km or so. This possibility may be ruled out because all the earthquakes in each source region yield a similar pattern of travel time residuals, even though the epicentre locations in each region are typically distributed over >200 km. Velocity

variations near the focus are further ruled out because early arrivals beyond 85° are not restricted to observations of deep earthquakes; they also occur, for example, in data from nuclear explosions in the Marshall Islands⁹.

Deep Mantle Structure

It seems, then, that lateral variations of compressional velocity in the middle or lower mantle are required to explain the travel time anomalies. But because of the uneven distribution of seismological observatories and deep earthquakes, the sampling of the mantle provided by available data is uneven, and it is impossible to determine uniquely the complete three dimensional velocity structure of the mantle. What can be determined is the average travel time residual for each of a number of "bundles" of rays following nearly identical paths from a seismic region to a group of stations, and from this information we infer the most probable cause of the variations. Table 1 summarizes the travel time data for all paths for which 9 or more observations are available. For each path a Student's t test has been used to evaluate the hypothesis that the mean travel time (after station corrections have been applied) is the value given by the curve in Fig. 1 and that deviations from this curve can be attributed to random measuring errors. Those ray paths for which the hypothesis could be rejected at the 99.5% confidence level are indicated in Table 1. Fig. 3 shows histograms of the residual distribution for these anomalous paths. For observations at distances beyond 70° , 16 paths (out of 34 tested) showed significant variations from the average curve, whereas for smaller distances, only 3 anomalous paths (out of 22) were found. This strongly suggests that most of the scatter originates in the deep mantle (depth $>2,000$ km). The possibility of the variations occurring at a shallower depth

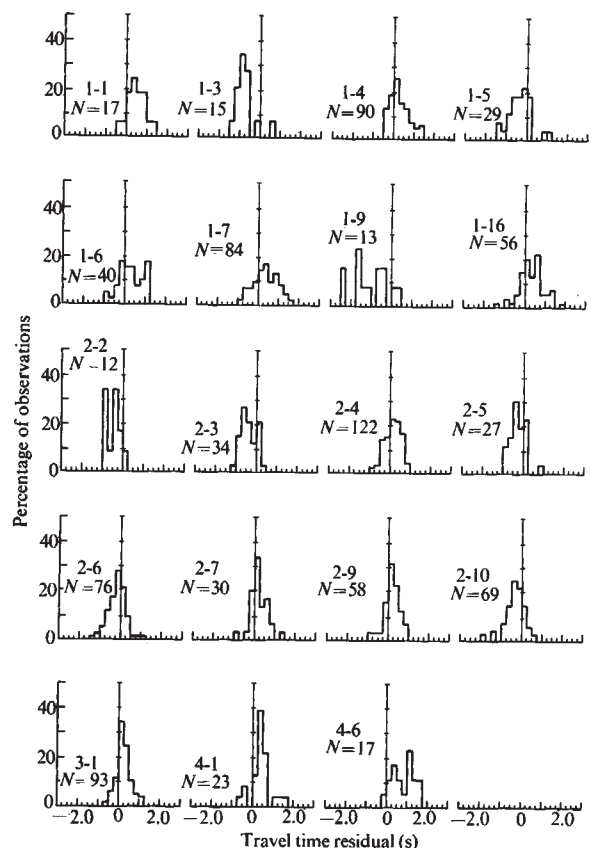


Fig. 3 Histograms of travel time residuals (relative to curve of Fig. 1 with station corrections applied) for different ray paths through the mantle. Identification numbers correspond to those in Table 1 and Fig. 4. N is the number of observations.

Table 1 Travel Time Statistics for Mantle P Wave Paths

Identification No.	<i>N</i>	$\bar{x}$	<i>s</i>	<i>t</i>	<i>t</i> _{99.5}	Path
(a) 85° < Δ < 100°						
1-1 *	17	0.46	0.43	4.41	3.25	Japan—USA
1-2	12	-0.11	0.56	-2.15	3.50	Bonin and Marianas Arc—USA
1-3 *	15	-0.76	0.48	-6.13	3.33	Tonga Arc—Alaska
1-4 *	90	0.23	0.50	4.37	2.89	Tonga Arc—Western North America
1-5 *	29	-0.34	0.57	-3.21	3.05	Argentina—Western North America
1-6 *	40	0.37	0.70	3.34	2.97	South America—Northwestern Europe
1-7 *	84	0.38	0.79	4.40	2.89	South America—Southern Europe
1-8	11	0.06	0.56	0.36	3.58	South America—Southern Africa
1-9 *	13	-1.09	0.91	-4.31	3.43	Kuril Arc—Spain, Morocco and Algeria
1-10	16	-0.36	0.58	-2.48	3.29	Bonin Arc—Europe
1-11	42	-0.19	0.65	-1.90	2.97	Indonesia and Philippine Is.—Central and Northern Europe
1-12	14	0.16	0.48	1.25	3.37	Indonesia and Philippine Is.—Middle East and Balkans
1-13	13	0.47	0.96	1.77	3.43	Indonesia and Philippine Is.—Central and Southern Africa
1-14	10	-0.12	0.56	-0.68	3.69	Tonga Arc—Siberia and China
1-15	9	-0.24	0.28	-2.57	3.83	Indonesia—Alaska
1-16 *	56	0.34	0.61	4.17	2.92	Solomon Is.—Western USA
1-17	29	0.04	0.33	0.65	3.05	New Hebrides—Western North America
(b) 70° < Δ < 85°						
2-1	57	-0.12	0.45	-2.02	2.92	Japan—USA
2-2 *	12	-0.51	0.36	-4.90	3.45	Japan—Southwestern USA
2-3 *	34	-0.38	0.37	-5.99	3.01	Bonin Arc—Western USA
2-4 *	122	0.16	0.40	4.38	2.86	Tonga Arc—Western North America
2-5 *	27	-0.27	0.39	-3.60	3.07	Kuril Arc—Eastern North America
2-6 *	76	-0.19	0.45	-3.68	2.90	Argentina and Bolivia—Central and Western USA
2-7 *	30	0.25	0.44	3.11	3.04	South America—Spain and Northern Africa
2-8	20	-0.09	0.45	-0.89	3.17	South America—Central and Southern Africa
2-9 *	58	0.19	0.43	3.36	2.92	Kuril Arc—Western Europe
2-10 *	69	-0.33	0.52	-5.28	2.91	Japan—Western Europe
2-11	22	0.02	0.36	0.26	3.14	New Hebrides—Western North America
2-12	20	-0.06	0.47	-0.57	3.17	Indonesia and Philippine Is.—Middle East
2-13	30	-0.09	0.52	-0.95	3.04	Bonin and Marianas Arcs—Scandinavia and Western Russia
2-14	23	0.14	0.38	1.77	3.12	Japan and Kuril Arc—Australia
2-15	11	-0.06	0.54	-0.37	3.58	Kuril Arc—Middle East
2-16	12	-0.39	0.56	-2.41	3.50	Indonesia—Antarctica
2-17	10	-0.22	0.25	-2.78	3.69	Marianas Arc—Western USA
2-18	12	-0.22	0.69	-1.10	3.50	Japan—Middle East
(c) 55° < Δ < 70°						
3-1 *	93	0.23	0.38	5.84	2.89	Kuril Arc—Western USA
3-2	45	0.12	0.40	2.01	2.96	Northern South America—Western USA
3-3	42	0.06	0.49	0.79	2.97	Bolivia and Argentina—Central USA
3-4	93	-0.05	0.54	-0.89	2.89	Kuril Arc and Sea of Japan—Northern and Eastern Europe and Middle East
3-5	30	-0.09	0.41	-1.20	3.03	Indonesia and Philippine Is.—Southwestern Asia
3-6	15	0.18	0.62	1.12	3.33	Japan and Kuril Arc—Melanesia
3-7	12	-0.04	0.41	-0.34	3.43	Tonga Arc—Western Australia
3-8	10	-0.28	0.45	-1.97	3.58	Japan and Kuril Arc—Australia
3-9	9	-0.19	0.55	-1.04	3.69	New Hebrides—China and Siberia
3-10	8	0.13	0.78	0.47	4.03	Solomon Is.—Japan
3-11	15	0.26	0.47	2.14	3.29	Tonga Arc—Antarctica
3-12	9	0.22	0.58	1.14	3.69	Indonesia—New Zealand
3-13	10	0.15	0.59	0.80	3.58	Indonesia—Antarctica
(d) 40° < Δ < 55°						
4-1 *	23	0.41	0.48	4.10	3.12	Kuril Arc—Northwestern North America
4-2	44	-0.18	0.48	-2.49	2.97	Northern South America—USA
4-3	15	0.35	0.41	3.31	3.33	Kuril Arc—Northern Europe
4-4	34	0.16	0.43	2.17	3.01	Japan—Southwestern Asia
4-5	17	-0.25	0.51	-2.02	3.22	Indonesia—India and Pakistan
4-6 *	17	0.82	0.56	6.03	3.25	Japan—Alaska
4-7	13	-0.51	0.65	-2.82	3.37	Indonesia—Japan and Korea
4-8	40	0.02	0.55	0.23	2.97	Indonesia—Southeastern Australia and Tasmania
4-9	20	-0.06	0.58	-0.46	3.15	Solomon Is.—Japan, Korea, and Eastern China

N = Number of observations. $\bar{x}$ = Mean travel time residual after station correction (*s*).*s* = Standard deviation of residuals (*s*).

$$t = \frac{\bar{x}}{s/\sqrt{N}}$$

*t*_{99.5} = 99.5% confidence limit for |*t*| if true mean is zero.

* Indicates paths with mean significantly different from zero.

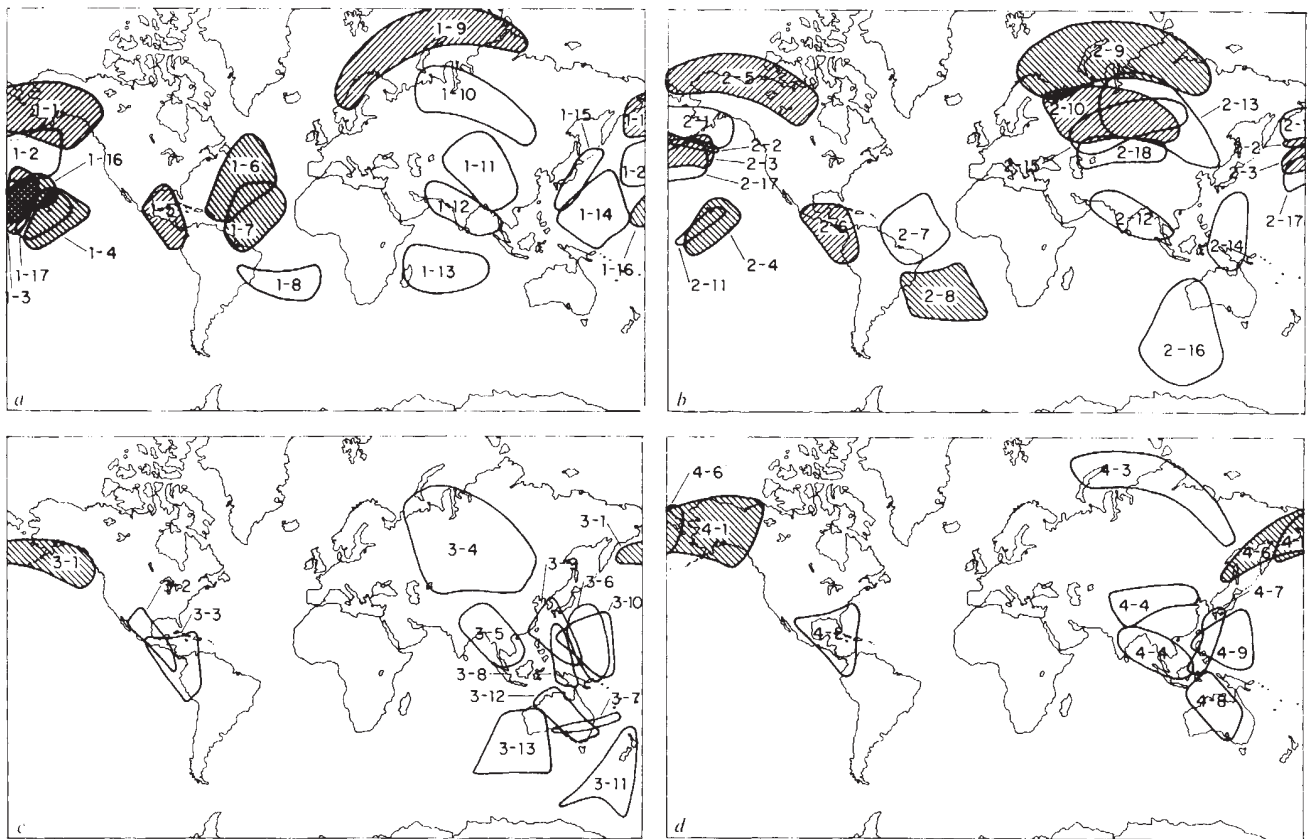


Fig. 4 Regions where paths of observed P waves bottom in the mantle. Cross-hatching indicates regions differing significantly from the mean determined from all data. Other regions tested are outlined. The identification numbers correspond to those in Table 1 and Fig. 3. ▨, Late; ▩, early.

cannot be absolutely disproved, but the velocity distribution in the Earth would have to be such that, given the distribution of earthquakes and seismic stations, all observed waves bottoming at the depth of the heterogeneities happen to be unaffected by them (even though P waves spend about 25% of their travel time traversing the lowest 10% of the ray path), while waves penetrating beneath the heterogeneities are affected. It seems unreasonable to assume such a conspiratorial behaviour on the part of the velocity variations when a much simpler hypothesis is available.

The actual details of the velocity distribution cannot, however, be determined precisely, because rays travel a great distance at approximately the same depth near their turning points. Fig. 4 shows the regions of the lower mantle sampled by the various ray bundles (defined arbitrarily as the central 30° of each path) and indicates which paths correspond to early and late arrivals. These are in most cases probably the regions where the actual velocity anomalies occur. Where regions overlap on the figure, they are generally consistent with each other (for example, regions 1-6 and 1-7, regions 2-2 and 2-3, and regions 4-1 and 4-6). This consistency is encouraging, in that it supports our argument that the travel time anomalies originate in the deep mantle and are not the result of some other type of systematic error. An apparent inconsistency exists between regions 1-3 and 1-16, but this is not surprising because of the uncertainty as to exactly where the travel time anomalies actually originate. The rays following path 1-3 also pass through regions 2-2 and 2-3 further to the north, and it is likely that the travel time anomaly actually originates there. Another interesting feature of Fig. 4 is a correlation between the anomalies in the two greatest distance ranges (for example, regions 1-7 and 2-7, regions 1-4 and 2-4, and regions 1-5 and 2-6), suggesting that the structure in the deep mantle has a spatial "coherence" of at least a few hundred km vertically.

The mean travel times in Table 1 show a variation of about 1.5 s for rays bottoming below 2,600 km, and about 0.6 s for rays bottoming between 2,000 and 2,600 km. These numbers are somewhat uncertain, but it is likely that the true travel times vary by at least 1 s. The amount by which the actual velocity in the mantle varies depends on the size of the regions within which the variations occur. The data of Fig. 4 suggest that the size of some of the anomalies, at least, is about 1,000 km or less, in which case the velocity must vary by at least 1%. This is a lower bound both because we have probably overestimated the scale of the inhomogeneities and because we are measuring averages of the velocity in rather large regions and some cancellation of the effects of positive and negative velocity anomalies is likely. Combined interpretation of travel time and $dT/d\Delta$ measurements can probably improve the resolution of structural details.

Might the deep mantle variations be related in some way to the convection plumes hypothesized by Wilson¹⁰ and Morgan¹¹ to exist in the deep mantle? To answer this the region of the Hawaiian Islands provides the best data, and here they indeed indicate a pronounced lateral variation, the velocities being high to the northwest of Hawaii (regions 2-2, 2-3, and probably 1-3) and low in the vicinity of the islands (regions 1-4, 2-4, and 1-6). Interestingly, the $dT/d\Delta$ data presented by Davies and Sheppard⁴ also indicate a horizontal velocity contrast of this sort in the vicinity of Hawaii. Unfortunately, no other proposed plumes are well sampled by our data. Region 1-13 includes the Mascarene Islands, but the data here are highly scattered, and no conclusion can be drawn. Regions 1-5 and 2-6, both with apparently high velocities, are located slightly to the northeast of the Galapagos Islands, so it is not clear what relation, if any, this velocity anomaly may bear to a possible plume. If travel time data for rays passing through more proposed plume regions can be obtained, they may

provide valuable evidence relevant to the Wilson–Morgan hypothesis.

Except, perhaps, for the Hawaiian Islands, no geological or tectonic features show an obvious correlation with the inferred deep mantle velocity anomalies. At shallower depths, however, this is not the case; regions 3–1, 4–1, and 4–6, all seeming to have low velocities, lie beneath the Kurile and Aleutian Island arcs. The only other island arc adequately sampled at these depths lies beneath Middle America (region 4–2) and is associated with early arrivals (though they are not significant at the 99.5% confidence level). The data thus suggest that low velocities may be characteristic of island arcs at depths greater than 1,000 km.

The data considered here do not support any correlation between velocity variations below 2,000 km and global gravity anomalies or geoid heights. At shallower depths such a correlation does exist, but it is merely another manifestation of the low velocities beneath the Kurile and Aleutian Islands, because the concave sides of island arcs are generally the sites of prominent positive free air gravity anomalies.

It is not possible to make a direct comparison between these results and those of Alexander and Phinney⁵. The region of the North Atlantic found by them to be anomalous is further east than the corresponding region sampled by our data. Further, travel time measurements such as ours provide a measure of

the average velocity in a region, whereas the behaviour of core diffracted waves depends on features such as the velocity gradient in the lower mantle. Further studies of variations in the “visibility” within the core shadow would be a useful complement to travel time and $dT/d\Delta$ studies of the lower mantle.

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- ¹ Toksöz, M. Nafi, Chinnery, M. A., and Anderson, D. L., *Geophys. J. Roy. Astron. Soc.*, **13**, 31 (1967).
- ² Hales, A. L., and Roberts, J. L., *Bull. Seismol. Soc. Amer.*, **60**, 1427 (1970).
- ³ Greenfield, R. J., and Sheppard, R. M., *Bull. Seismol. Soc. Amer.*, **59** (1969).
- ⁴ Davies, D., and Sheppard, R. M., *Nature*, **239**, 318 (1972).
- ⁵ Alexander, Shelton S., and Phinney, R. A., *J. Geophys. Res.*, **7**, 5943 (1966).
- ⁶ Sengupta, Mrinal K., thesis, MIT (1972).
- ⁷ Herrin, E., Tucker, W., Taggart, J., Gordon, D. W., and Lobdell, J. L., *Bull. Seismol. Soc. Amer.*, **58**, 1273 (1968).
- ⁸ Lilwal, R. C., and Douglas, A., *Geophys. J. Roy. Astron. Soc.*, **19**, 165 (1970).
- ⁹ Carder, D. S., Gordon, D. W., and Jordan, J. N., *Bull. Seismol. Soc. Amer.*, **56**, 815 (1966).
- ¹⁰ Wilson, J. T., *Phil. Trans. Roy. Soc., A*, **258**, 145 (1965).
- ¹¹ Morgan, W. J., *Nature*, **230**, 42 (1971).

Evidence for an Advanced Plio-Pleistocene Hominid from East Rudolf, Kenya

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Four specimens collected last year from East Rudolf are provisionally attributed to the genus *Homo*. One, a cranium KNM-ER 1470, is probably 2.9 million years old.

PRELIMINARY descriptions are presented of four specimens collected from East Rudolf during 1972. Most of the collection recovered during this field season has been reported recently in *Nature*¹; the specimens described here are sufficiently important to be considered separately and in more detail. The collections of fossil hominids recovered from East Rudolf during earlier field seasons and detailed descriptions of some of these specimens have been published previously^{2–5}.

The specimens described here are: (1) a cranium, KNM-ER 1470; (2) a right femur, KNM-ER 1472; (3) a proximal fragment of a second right femur, KNM-ER 1475; and (4) an associated left femur, distal and proximal fragments of a left tibia, and a distal left fibula, KNM-ER 1481. They were all recovered from area 131 (see Fig. 1) and from deposits below the KBS Tuff which has been securely dated at 2.6 m.y.⁶.

Area 131 consists of approximately 30 km² of fluvial and lacustrine sediments. The sediments are well exposed and show no evidence of significant tectonic disturbance; there is a slight

westward dip of less than 3°. Several prominent marker horizons provide reference levels and have permitted physical correlation of stratigraphical units between area 131 and other areas in the East Rudolf locality.

Several tuffs occur in the vicinity of area 131. The lowest of these is the Tulu-Bor Tuff which is not exposed in the area itself but does outcrop nearby in several stream beds. Above this horizon, in a composite section, there is some 60 m of sediment capped by the prominent KBS Tuff. This latter tuff has been mapped into areas 108 and 105 (also shown in Fig. 1) from where samples have been obtained for K/Ar dates. An account of the geology is given by Vondra and Bowen⁷. A section showing the vertical position of these four hominids in relation to the KBS Tuff is given in Fig. 2.

At present, analysis of samples collected for dating from the KBS Tuff in area 131 has proved inconclusive because of the apparent alteration of the sanidine feldspars. This was not seen in the 105/108 samples from the same horizon which provided the date of 2.61 m.y. and there is no reason to suspect the validity of that date (personal communication from J. A. Miller).

Detailed palaeomagnetic investigation of the sedimentary units is being undertaken by Dr A. Brock (University of Nairobi). Systematic sampling closely spaced in the section has identified both the Mammoth and Kaena events in area 105 between the Tulu-Bor and KBS Tuffs, a result which supports the 2.61 m.y. date on the latter. The mapping of several

horizons has established a physical correlation between areas 105 and 131. During the 1973 season, the area 131 succession will be sampled in detail in an attempt to confirm this correlation. Available evidence points to a probable date of 2.9 m.y. for the cranium KNM-ER 1470, and between 2.6 and 2.9 m.y. for the other specimens reported here.

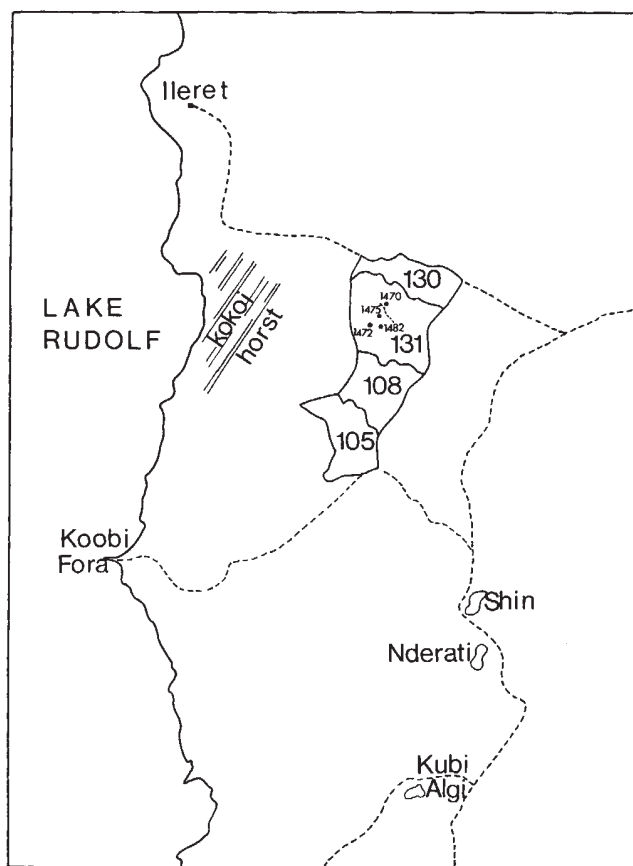


Fig. 1 Map showing sites of discovery of fossil hominids KNM-ER 1470, 1472, 1475 and 1481 in the East Rudolf locality. Succession shown in Fig. 2 was taken from the position indicated by the dotted line.

Collections of vertebrate fossils recovered from below the KBS Tuff in areas 105, 108 and 131 all show the same stage of evolutionary development and this evidence supports the indicated age for this phase of deposition at East Rudolf. Maglio⁸ has discussed the fossil assemblages following detailed studies of field collections from various horizons.

The cranium (KNM-ER 1470) and the postcranial remains (KNM-ER 1472, 1475 and 1481) were all recovered as a result of surface discovery. The unrolled condition of the specimens and the nature of the sites rules out the possibility of secondary deposition—there is no doubt in the minds of the geologists that the provenance is as reported. All the specimens are heavily mineralized and the adhering matrix is similar to the matrix seen on other fossils from the same sites. In due course, microscopic examination of thin sections of matrix taken from the site and on the fossils might add further evidence.

Cranium KNM-ER 1470

Cranium KNM-ER 1470 was discovered by Mr Bernard Ngeneo, a Kenyan, who noticed a large number of bone fragments washing down a steep slope on one side of a gully.

Careful examination showed that these fragments included pieces of a hominid cranium. An area of approximately 20 m × 20 m was subsequently screened and more than 150 fragments were recovered.

The skull is not fully reconstructed. Many small fragments remain to be included and it may be some time before the task is completed. At present the cranial vault is almost complete and there are good joins between the pieces. The face is less complete and although there are good contacts joining the maxilla through the face to the calvaria, many pieces are still missing. The orientation of the face is somewhat uncertain because of distortion of the frontal base by several small, matrix filled cracks. The basicranium shows the most damage and is the least complete region.

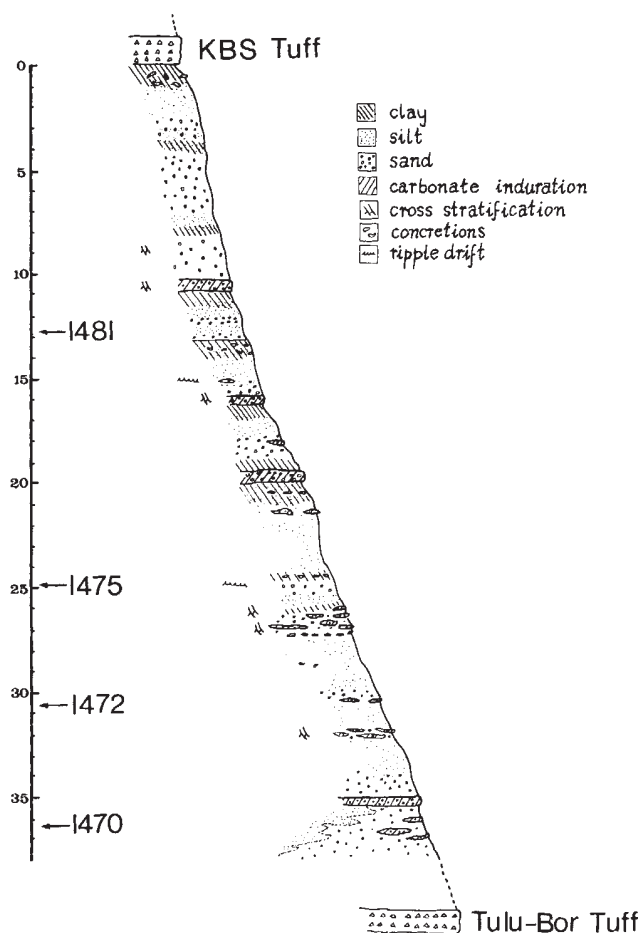


Fig. 2 Stratigraphical succession of the sediments in area 131 and the vertical relationships of the fossil hominids KNM-ER 1470, 1472, 1475 and 1481 to the KBS Tuff. Dotted line shown in Fig. 1 marks the position at which the section was taken.

The cranium (see Fig. 3) shows many features of interest. The supraorbital tori are weakly developed with no continuous supratral sulcus. The postorbital waisting is moderate and there is no evidence of either marked temporal lines or a temporal keel. The vault is domed with steeply sloping sides and parietal eminences. The glenoid fossae and external auditory meati are positioned well forward by comparison with *Australopithecus*. The occipital area is incomplete but there is no indication of a nuchal crest or other powerful muscle attachments.

In view of the completeness of the calvaria, it has been pos-

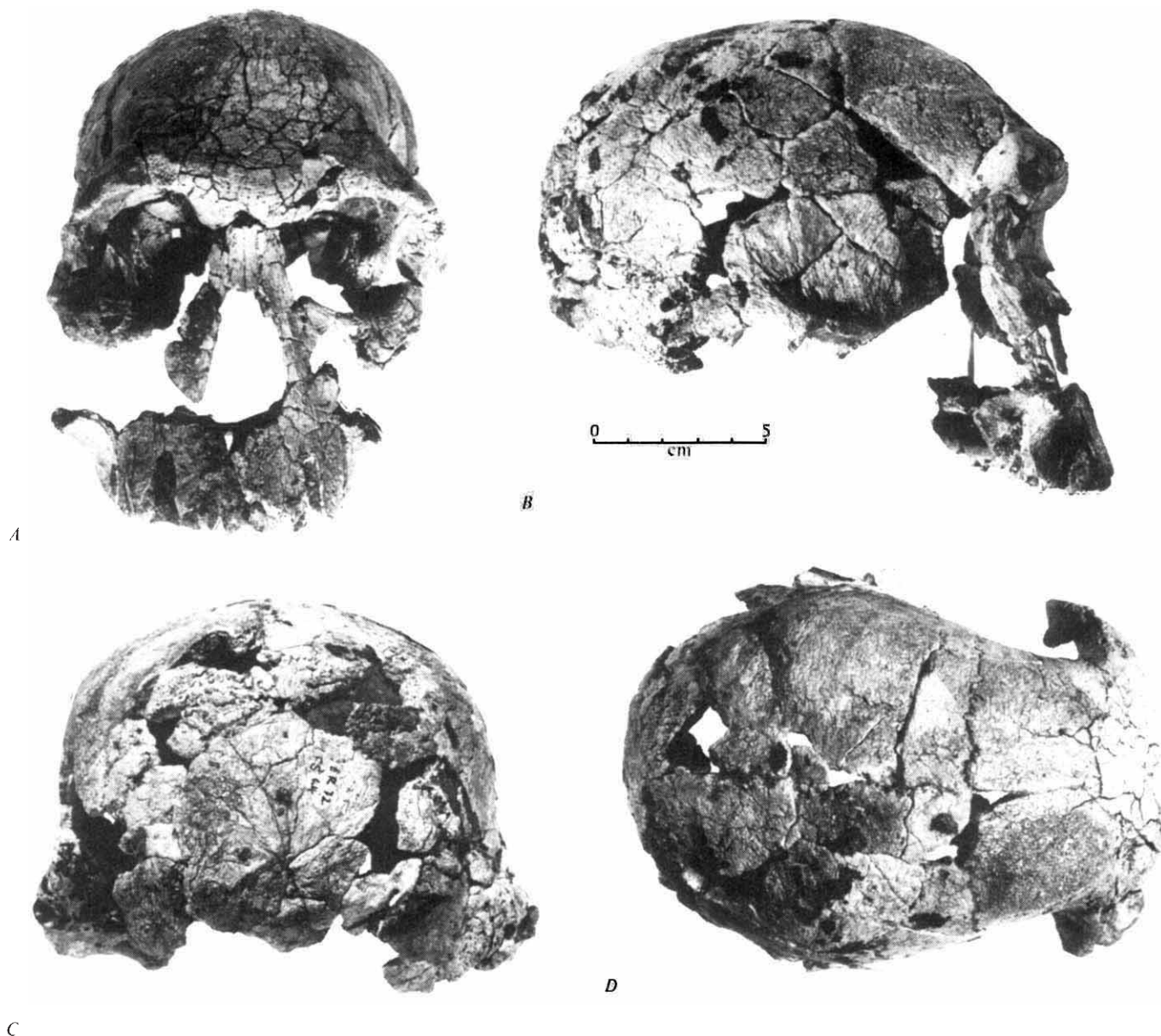


Fig. 3 Cranium KNM-ER 1470. *a*, Facial aspect; *b*, lateral aspect; *c*, posterior aspect; *d*, superior aspect.

sible to prepare in modelling clay an endocranial impression which has been used to obtain minimum estimates for the endocranial volume. Six measurements of the endocast by water displacement were made by Dr A. Walker (University of Nairobi), and gave a mean value of 810 cm³. Further work on this will be undertaken but it seems certain that a volume of greater than 800 cm³ for KNM-ER 1470 can be expected.

The palate is shallow, broad and short with a nearly straight labial border that is reminiscent of the large *Australopithecus*. The great width in relationship to the length of the palate does contrast markedly, however, with known australopithecine material. The molars and premolar crowns are not preserved, but the remaining roots and alveoli suggest some mesiodistal compression. The large alveoli of the anterior teeth suggest the presence of substantial canines and incisors.

Femur KNM-ER 1472

KNM-ER 1472, a right femur, was discovered as a number of fragments by Dr J. Harris. It shows some features that are also seen in the better preserved left femur, KNM-ER 1481, but other features, such as the apparently very straight shaft and

the bony process on the anterior aspect of the greater trochanter, require further evaluation.

Femoral Fragment KNM-ER 1475

The proximal fragment of femur, KNM-ER 1475, was discovered by Mr Kamoya Kimeu. Its condition is such that a final taxonomic identification will be difficult and it is therefore included only tentatively in this report. This fragment shows some features such as a short, more nearly cylindrical neck, which are not seen in the femurs of *Australopithecus*.

Associated Skeleton KNM-ER 1481

A complete left femur, KNM-ER 1481, associated with both ends of a left tibia and the distal end of a left fibula were also discovered by Dr J. Harris.

The femur (see Fig. 4) is characterized by a very slender shaft with relatively large epiphyses. The head of the femur is large and set on a robust cylindrical neck which takes off from

the shaft at a more obtuse angle than in known *Australopithecus* femurs. There is a marked insertion for gluteus maximus and the proximal region of the shaft is slightly flattened antero-posteriorly. The femoro-condylar angle is within the range of *Homo sapiens*. When the femur is compared with a restricted sample of modern African bones, there are marked similarities in those morphological features that are widely considered characteristic of modern *H. sapiens*. The fragments of tibia and fibula also resemble *H. sapiens* and no features call for specific comment at this preliminary stage of study.

Homo or *Australopithecus* ?

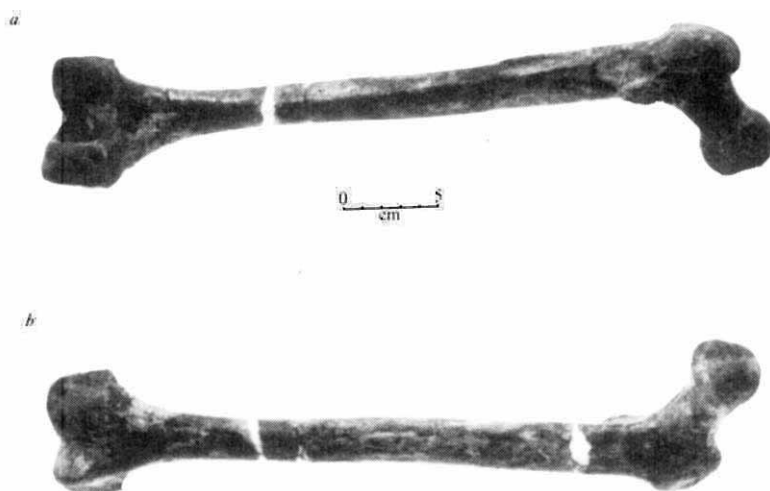
The taxonomic status of the material is not absolutely clear, and detailed comparative studies which should help to clarify

(ref. 10). The Olduvai material is only known from deposits that are stratigraphically above a basalt dated at 1.96 m.y. (ref. 11). At present therefore there does not seem to be any compelling reason for attributing to this species the earlier, larger brained, cranium from East Rudolf.

The 1470 cranium is quite distinctive from *H. erectus* which is not certainly known from deposits of equivalent Pleistocene age. It could be argued that the new material represents an early form of *H. erectus*, but at present there is insufficient evidence to justify this assertion.

There is no direct association of the cranial and postcranial parts at present, and until such evidence becomes available, the femora and fragment of tibia and fibula are only provisionally assigned to the same species as the cranium, KNM-ER 1470. Differences from the distinctive *Australopithecus* postcranial elements seem to support this inferred association.

Fig. 4 Left femur KNM-ER 1481. *a*, Posterior aspect; *b*, anterior aspect.



this problem have yet to be concluded. The endocranial capacity and the morphology of the calvaria of KNM-ER 1470 are characters that suggest inclusion within the genus *Homo*, but the maxilla and facial region are unlike those of any known form of hominid. Only the flat fronted wide palate is suggestive of *Australopithecus*, but its extreme shortening and its shallow nature cannot be matched in existing collections representing this genus. The postcranial elements cannot readily be distinguished from *H. sapiens* if one considers the range of variation known for this species.

The East Rudolf area has provided evidence of the robust, specialized form of *Australopithecus* from levels which span close to 2 m.y. (2.8 m.y.–1.0 m.y.)¹; throughout this period the morphology of this hominid is distinctive in both cranial and postcranial elements. The cranial capacity of the robust australopithecine from Olduvai Gorge, *A. boisei*, has been estimated for OH 5 to be 530 cm³ (ref. 9); this is the same value as that estimated by Holloway for the only specimen in South Africa of *A. robustus* which provides clear evidence of cranial capacity⁹. Holloway has also found the mean cranial capacity of six specimens of the small gracile *A. africanus* from South Africa¹⁰ to be 422 cm³. Thus, to include the 1470 cranium from East Rudolf within the genus *Australopithecus* would require an extraordinary range of variation of endocranial volume for this genus. This seems unacceptable and also other morphological considerations argue strongly against such an attribution.

The Olduvai Gorge has produced evidence of an hominine, *H. habilis*; the estimated endocranial volumes for three specimens referred to this species are 633, 652 and 684 cm³

For the present, I propose that the specimens should be attributed to *Homo* sp. indet. rather than remain in total suspense. There does not seem to be any basis for attribution to *Australopithecus* and to consider a new genus would be, in my mind, both unnecessary and self defeating in the endeavour to understand the origins of man.

I should like to congratulate Mr Ngeneo and Dr Harris for finding these important discoveries. Dr Bernard Wood spent many long hours at the site screening for fragments and assisted my wife, Meave, and Dr Alan Walker in the painstaking reconstruction work. I thank them all. The support of the National Geographic Society, the National Science Foundation, the W. H. Donner Foundation and the National Museum of Kenya is gratefully acknowledged.

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¹ Leakey, R. E. F., *Nature*, **242**, 170 (1973).

² Leakey, R. E. F., *Nature*, **231**, 241 (1971).

³ Leakey, R. E. F., *Nature*, **237**, 264 (1972).

⁴ Leakey, R. E. F., Mungai, J. M., and Walker, A. C., *Amer. J. Phys. Anthropol.*, **35**, 175 (1971).

⁵ Leakey, R. E. F., Mungai, J. M., and Walker, A. C., *Amer. J. Phys. Anthropol.*, **36**, 235 (1972).

⁶ Fitch, F. J., and Miller, J. A., *Nature*, **226**, 223 (1970).

⁷ Vondra, C., and Bowen, B., *Nature*, **242**, 391 (1973).

⁸ Maglio, V. J., *Nature*, **239**, 379 (1972).

⁹ Tobias, P. V., *The Brain in Hominid Evolution* (Columbia University Press, New York and London, 1971).

¹⁰ Holloway, R. L., *Science*, **168**, 966 (1970).

¹¹ Curtis, G. H., and Hay, R. L., in *Calibration of Hominoid Evolution* (edit. by W. W. Bishop and J. A. Miller) (Scottish Academic Press, Edinburgh, 1972).

LETTERS TO NATURE

PHYSICAL SCIENCES

Oceanic Observation of New York Bight by ERTS-1

ON August 16, 1972, the multispectral scanner (MSS) aboard the first Earth Resources Technology Satellite (ERTS) obtained images of New York Bight which contain information of oceanographic significance. The images demonstrate the effectiveness of satellite use in observing surface features that indicate variations of water quality.

The MSS measures reflectance of solar energy in four channels with band pass filters that cover visible and near infrared bands from 0.5 to 1.1 μm . Because solar energy penetrates ocean water further for the shorter observed wavelengths, features characteristic of the water mass, such as turbidity, are more predominant in the lower bands; features on or above the sea surface, such as clouds, tend to appear with uniform strength in all channels (Fig. 1). A nearly perfect target at 5 m will reflect 50% of the energy in the lowest band and essentially none in the highest band.

Fig. 2 shows imagery from the band most sensitive to ocean features—MSS-5; MSS-4 is partly obscured with haze induced by atmospheric scatter. The most prevalent oceanic feature in this frame is visibly turbid surface water near the coast. A plume of light-coloured water extends from the New York harbour complex south along the New Jersey coast. The plume, approximately 18 mile long and 7 mile wide, represents the offshore Hudson River effluent. The Hudson River plume is relatively small at this time of year owing to reduction in the outflow of fresh water and is pushed on to the New Jersey coast by the prevailing winds.

Inhomogeneities in the plume indicate the turbulent mixing

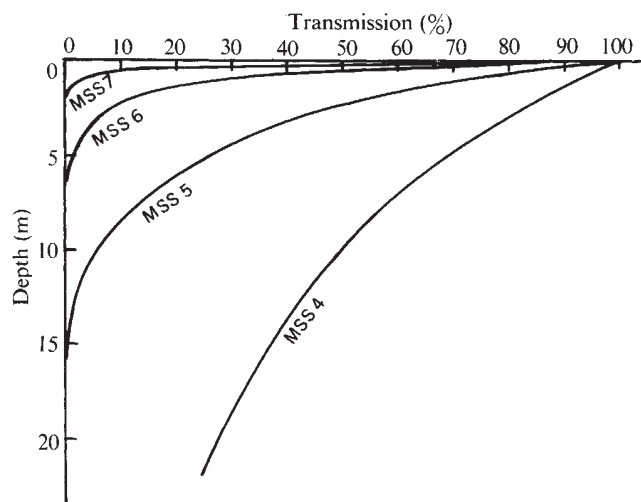


Fig. 1 Theoretical calculation of the proportion of solar energy penetrating the sea surface that reaches a given depth for each of the four channels of the ERTS MSS. Calculations used the attenuation coefficient for pure water. This provides a conservative estimate because for the cleanest sea water α is much larger.

processes by which plume water is absorbed into ambient Bight water. The relatively sharp eastern boundary of the plume suggests that dispersion processes are not isotropic.

There are features in the Bight apex about 20 mile southeast of the harbour entrance, seemingly manifestations of human activity in the area. A line and a more diffuse circular patch north of the line are seen in this frame. These features are located in the general area used for waste disposal¹.

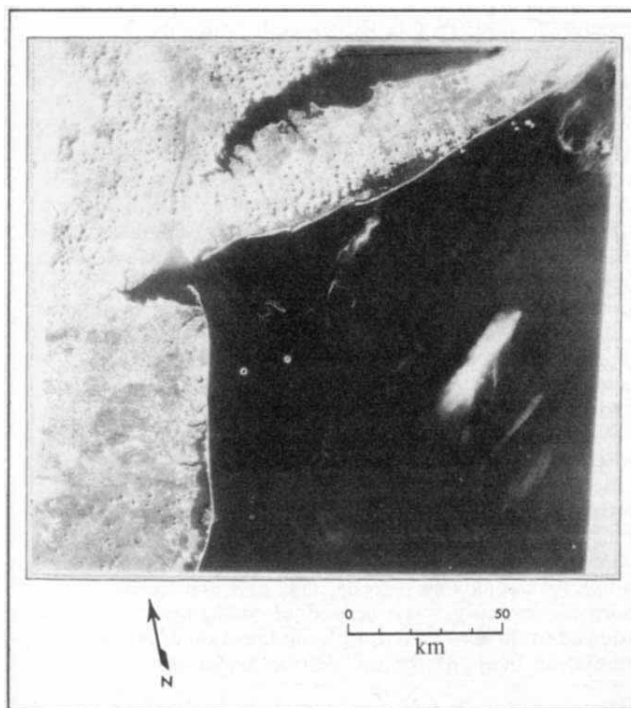


Fig. 2 Bulk processed imagery in the 0.6 to 0.7 μm band of ERTS-1 from the New York Bight transit of August 16, 1972.

The line resulted from the disposal of waste acid. Less distinct portions of the line may be the residue of an earlier dump, at least 12 h before; dispersion has evidently been slow. Even though wind mixing was low for that day it is apparent that dumping of this magnitude will usually produce a persistent surface feature. Subsequent ERTS images all show dump residues.

The diffuse circular patch to the north of the waste acid dump is close to the sewer sludge dump site. Surface vestige of a sewer sludge dump is much less noticeable than waste acid; only a grey-brown slick remains. Initial low intensity of reflected light makes the character of the surface patch less discernible.

It seems likely that satellites with sensors optimized to view the ocean in visible and infrared wavelengths, supplying synoptic data over large areas, will materially aid management of the coastal zone on a broad scale.

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¹ *Effects of Waste Disposal in the New York Bight* (National Marine Fisheries Service, Sandy Hook, New Jersey, 1972).

Organic Mercury Compounds in Coastal Waters

ORGANIC mercury compounds have been demonstrated in biological material¹⁻³ and the pioneering work of Jensen and Jernelov⁴⁻⁶ and Wood, Rosen and Kennedy⁷ has demonstrated that these organic mercury compounds can be synthesized by microorganisms in fresh water sediments. Their studies strongly suggest that organic compounds of mercury may be present in natural waters, although there is little experimental evidence for the existence of organic forms of Hg in either fresh or marine water. The role of mercury and its ultimate fate in fresh or marine environments will depend on its chemical and physical form. Thus, a meaningful assessment of the effects of toxic or latently toxic metals, such as mercury, on the biosphere requires identification and differentiation of the various chemical species of the metal in the environment. Here we present experimental data indicating the presence of organic forms of mercury in river water and in coastal seawater, and we hope to encourage further study of the role of mercury in natural waters.

We have determined total and inorganic mercury in coastal waters and adjacent river waters in the vicinity of Long Island Sound. The mercury determinations were made on two different sets of 100 ml. aliquots of natural water. Both sets of samples were collected in glass bottles and acidified to pH 1.0 with redistilled concentrated nitric acid. The first set of samples was analysed directly, and gave the concentration of inorganic mercury. The second set of samples was photo-oxidized for at least 24 h using a modification of the ultraviolet-irradiation method⁸ for the destruction of dissolved organic

carbon in natural waters⁹. These aliquots were then analysed, and this measurement gives the total amount of mercury present. The total mercury minus inorganic equals the mercury associated organically.

Mercury was measured by a modification of the standard flameless atomic absorption technique¹⁰. That is, a simple but effective non-contaminating method for concentrating Hg before its passage through the gas cell was developed and employed for these determinations. After reduction Hg is trapped while purging (N₂ gas) and concentrated on a packed column ('Chromosorb' WHP; 80/100 mesh, 1.5% OV-17 and 1.95% QF-1) immersed in a liquid nitrogen bath¹¹. When purging is complete, the column is removed from the cold trap, heated and the gas phase absorption (2537 Å) of the eluted Hg is measured using a 'Coleman' Hg analyser (MAS-50). A detection limit of 0.0017 µg Hg l.⁻¹ is obtained using a ×20 scale expansion on the recorder.

Table 1 Mercury Fractions in Long Island Sound Waters

Location	Date of collection	Salinity ‰	Mercury concentration (µg l. ⁻¹)		
			Total*	Inor- ganic†	Or- ganic
Connecticut River	August 21, 1972	0.09	0.045	0.021	0.024
Avery Point Dock Water	September 26, 1972	29.7	0.067	0.025	0.042
Fishers Island Sound	August 17, 1972	30.1	0.078	0.028	0.050
Race, Long Island Sound	October 13, 1972	30.3	0.047	0.033	0.014

* Amount of Hg measured in the organic free (photo-oxidized) acidified water samples.

† Amount of Hg measured in the raw acidified water samples.

The precision of analysis for Hg is 15% based on repeats of a standard sample (concentration at 0.025 µg Hg l.⁻¹) and reported as a coefficient of variation. The samples were not filtered and the concentrations reported include the contribution of acid leachable mercury associated with particulate material. Some of this mercury solubilized by the acid treatment may be in an organically associated form, and this quantity will appear in our total mercury measurements. Burton and Leatherland¹² found the acid leachable portion to be not greater than 10% of the total measurable mercury in the dissolved form. As yet, we have not analysed particulate matter for its mercury content or fractions.

The concentrations of inorganic, organic and total mercury found in this study are given in Table 1. It is most significant

Table 2 Summary of Mercury Determinations in Seawater

Ocean region	Date of report	Mercury concentration	Experimental method	Reference
North Sea	1934	0.03 µg l. ⁻¹	Electrochemical following co-precipitation with CuS	(13)
Ramapo Deep—off Japan	1961	0.08–0.25 µg l. ⁻¹	Spectrophotometry after dithizone extraction	(14)
British Coastal Waters	1971	0.011–0.021 µg l. ⁻¹	Spectrophotometry after anion exchange concentration	(12)*
North Atlantic	1971	0.003–0.020 µg l. ⁻¹	As reference 12	(15)
Canadian Continental Shelf	1972	0.058–0.071 µg/kg	Gas phase atomic absorption spectrophotometry	(16)†
Pacific Ocean: off Coast of Mexico	1972		Thermal neutron activation after co-precipitation with CuS	(17)
60 km		0.022–0.153 µg/kg		
150 km		0.012–0.025 µg/kg		
Greenland Sea	1972	0.016–0.364 µg l. ⁻¹	Gas phase atomic absorption spectrometry after Au amalgamation	(18)

* British river waters were found to contain 0.009–0.010 µg Hg l.⁻¹.

† Along a Nova Scotian estuary, 0.046–0.201 µg Hg kg⁻¹ was measured.

that as much as 50–60% of the mercury present in these waters (river and coastal seawater) may exist either as organic compounds or in association with the organic matter (Table 1). This determination of mercury associated with organic material is from an indirect gross measurement of the contribution of mercury liberated from the total organic background. At present, we have no idea of how Hg is bound in the chemical species making up the organic mercury portion.

Previous investigations of mercury in the marine environment have been concerned principally with total mercury concentrations. The reported amounts for Hg in seawater vary from 0.003 to 0.364 $\mu\text{g l}^{-1}$ (Table 2). Our data are certainly within this broad range, but much of the mercury may be present in organically associated forms that are not always reactive or measurable by the commonly employed techniques. Apart from normal analytical consideration, it is difficult therefore to evaluate and comment on available Hg data in natural waters. This analytical anomaly will vary with technique and even within a study if the organic background is changing.

The work tabulated in Table 2 and our determinations suggest that regional differences exist for the mercury concentrations in the coastal marine environment. It would appear, for example, that concentrations of Hg reported for British coastal waters are significantly lower than those found in Long Island Sound or the Canadian Shelf waters. As noted, however, there are still uncertainties about the types and amounts of the various mercury species present in marine waters and the fraction being measured. This information will be required to determine more accurately the mercury distribution in the oceans and to elucidate the pathways and interactions of mercury in the estuarine and marine environment. Every effort should be made to develop methods capable of differentiating the various chemical forms of mercury in natural waters.

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- ¹ Westoo, G., *Acta Chem. Scand.*, **20**, 2131 (1966).
- ² Westoo, G., *Acta Chem. Scand.*, **21**, 1790 (1967).
- ³ Westoo, G., in *Chemical Fallout* (edit. by Miller, M. W., and Berg, G. G.), 75 (Thomas, Springfield, 1969).
- ⁴ Jensen, S., and Jernelov, A., *Nordforsk Biocindenformation*, No. 10, March (1967).
- ⁵ Jensen, S., and Jernelov, A., *Nordforsk Biocindenformation*, No. 14, February (1968).
- ⁶ Jensen, S., and Jernelov, A., *Nature*, **223**, 753 (1969).
- ⁷ Wood, J. M., Rosen, C. G., and Kennedy, S. F., *Nature*, **220**, 173 (1968).
- ⁸ Armstrong, F. A. J., Williams, P. M., and Strickland, J. D. H., *Nature*, **211**, 481 (1966).
- ⁹ Fitzgerald, W. F., thesis, MIT and WHOI (1970).
- ¹⁰ Hatch, W. R., and Ott, W. L., *Anal. Chem.*, **40**, 2085 (1968).
- ¹¹ Fitzgerald, W. F., Hunt, C. D., and Lyons, W. B., in *Baseline Studies of Pollutants in the Marine Environment (Heavy Metals) Halogenated Hydrocarbons and Petroleum*, Background Papers for a Workshop Sponsored by the NSF Office for the IDOE, Brookhaven Natl. Lab., May 24–26, 1972.
- ¹² Burton, J. D., and Leatherland, T. M., *Nature*, **231**, 440 (1971).
- ¹³ Stock, A., and Cucuel, F., *Naturwissenschaften*, **22**, 390 (1934).
- ¹⁴ Hosohara, K. J., *Chem. Soc. Jap., Pure Chem. Sect.*, **82**, 1107 (1961).
- ¹⁵ Leatherland, T. M., Burton, J. D., McCartney, M. J., and Culklin, F., *Nature*, **232**, 112 (1971).
- ¹⁶ Cranston, R. E., and Buckley, D. E., *Envir. Sci. Technol.*, **6**, 274 (1972).
- ¹⁷ Weiss, H. V., Yamamoto, S., Crozier, T. E., and Mathewson, J. H., *Envir. Sci. Technol.*, **6**, 644 (1972).
- ¹⁸ Carr, R. A., Hoover, J. B., and Wilkniss, P. E., *Deep-Sea Res.*, **19**, 747 (1972).

Fine Structure in the X-ray Emission Spectrum of N_2 , Compared with Electron Spectroscopy

X-RAY emission spectroscopy has considerable potential in studying the valence electron structure of matter, and has been used to examine the electronic band structure of solids. To a much lesser extent it has been applied to the study of molecular orbitals in free molecules, but owing to lack of resolution in the experimental spectra it is difficult to discern very well the different valence orbitals in a molecule. These orbitals have instead been observed and studied in great detail by other techniques, among which electron spectroscopy (ESCA) has been successful in elucidating both valence electron orbitals and core electron orbitals^{1,2}. If X-ray transitions involving molecular valence electrons could conveniently be examined with a resolution of 1 eV or better there should be many applications for these types of study. We have constructed an apparatus for this purpose in which the X-ray emission spectra from gaseous samples are excited by electron impact and analysed in a grazing incidence grating spectrometer at a resolving power of 3,000^{3,4}. This corresponds to ≈ 0.1 eV for the characteristic X-radiation of the second period elements. We show here that such high resolution in the X-ray spectrum reveals the molecular orbital structure and molecular states in sufficient detail to allow direct comparisons with molecular ESCA spectra and lets us observe fine structure due to molecular vibration in an X-ray line. Dipole selection rules control the X-ray transitions and serve as a guide in the assignment of the different valence orbitals of the molecule.

We used the nitrogen molecule in our investigation. The N_2 emission spectrum was recorded in 1st, 2nd, 3rd and higher orders on 'Kodak SWR' plates. In some of the exposures the Mo M_γ line was also recorded as an energy reference. The nitrogen X-ray emission spectrum is shown in Fig. 1 together with the electron spectrum excited with both AlK_α and HeI radiation. From the value for the Mo M_γ line (192.55 ± 0.05 eV) given in ref. 5 the N_2 lines were determined using the dispersion of the instrument. The energies thus established are presented in Table 1.

Table 1 Energies and Assignments of the Lines in the X-ray Spectrum of N_2

	Energy		Relative energy		Assignment
	X-ray	ESCA ^{1,2}	X-ray	ESCA ^{1,2}	
1	400.81	400.8*			$\text{N}1s \leftarrow 1\pi_g$
2	400.27				Transitions in doubly ionized or singly ionized, excited N_2
3	399.74				
4	399.04				
5	397.14				
6	394.40	394.3	0.00	0.00	$\text{N}1s \leftarrow 3\sigma_g (\text{X}^2\Sigma_g^+)$
7	394.17		-0.23	-0.26	
8	393.34†	393.2	-1.06	-1.12	$\text{N}1s \leftarrow 1\pi_u (\text{A}^2\Pi_u)$
9	391.33	391.1	-3.07	-3.18	$\text{N}1s \leftarrow 2\sigma_u (\text{B}^2\Sigma_u^+)$
10	384.5 ± 0.5	385.0	-8.9	-9.7‡	$\text{N}1s \leftarrow (\text{C}^2\Sigma_u^+)$
11	381.3 ± 0.5	381.3	-13.1	-13.0	
12	378.1 ± 0.5	377.9	-16.3	-16.4	
13	372.1 ± 0.5	372.6	-22.3	-21.8	$\text{N}1s \leftarrow 2\sigma_g (\text{X}^2\Sigma_g^+)$

Energies are expressed in eV, and the energies relative to the $3\sigma_g$ line are generally determined with an accuracy of ± 0.10 eV or better.

* From ref. 7.

† Refers to the line of highest energy in the band.

‡ From refs. 1 and 6.

The ground state configuration of N_2 is $1\sigma_g^2 1\sigma_u^2$ ($\text{N}1s$) $2\sigma_g^2 2\sigma_u^2 1\pi_u^4 3\sigma_g^2$; $^1\Sigma_g^+$ with $1\pi_g$ orbital as the first empty valence orbital. Fig. 1 and Table 1 show that the X-ray transitions involving the valence orbitals can be identified from a direct comparison between ESCA results and the present ones. The strongest lines (numbers 6, 7, 8, 9 in Fig. 1) are shown with higher resolution in the densitometer curve of the third order spectrum in Fig. 2. These lines correspond to the transitions

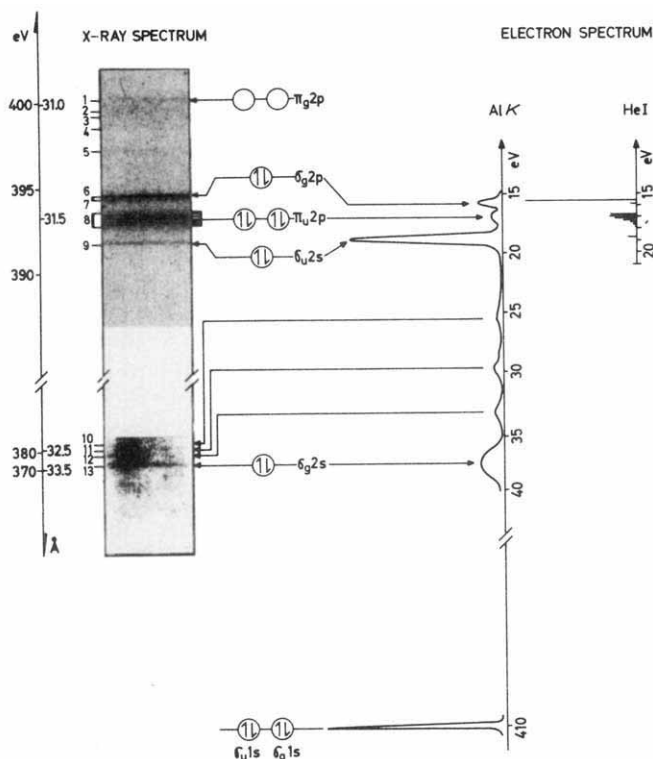


Fig. 1 The X-ray spectrum of N_2 together with the electron spectra excited with the $AlK\alpha$ and HeI radiations. In the X-ray spectrum the energy region 370–385 eV is shown with a compressed energy scale as compared to the 390–400 eV region.

$N1s \rightarrow 3\sigma_g$, $1\pi_u$ and $2\sigma_u$ and it is obvious from Fig. 2 that the first two of them exhibit fine structure. The $3\sigma_g$ line consists of a strong line with a weaker component at 0.23 eV lower energy, while the $1\pi_u$ line is composed of a progression of lines with an average spacing of 0.20 eV. The spacings between the lines are in excellent agreement with the vibrational splittings in the HeI electron spectrum. We conclude therefore that this fine structure in the X-ray lines can be ascribed to vibrational splittings as has been presented elsewhere (unpublished manuscript). To our knowledge such fine structure within X-ray emission lines has not been observed before.

The profile of the $3\sigma_g$ line confirms that it is a slightly bonding or nearly nonbonding orbital, while the wide envelope of the $1\pi_u$ line agrees with its strongly bonding character. The $2\sigma_u$ line is narrow as can be expected, as this orbital is nominally antibonding. These X-ray lines derive their intensities from the $N2p$ population of the corresponding valence orbitals whereas in the electron spectra both s and p populations contribute, although with different photoelectric cross sections. The $N1s \rightarrow 2\sigma_g$ transition can be seen in Fig. 1 as a broad line (No. 13). The $2\sigma_g$ orbital is considerably broadened (≈ 3 eV) as can also be seen in the electron spectrum. This orbital has about the same $N2p$ character as the $2\sigma_u$ orbital and one would therefore expect almost equal intensity for the X-ray transitions leading to vacancies in these orbitals.

At least three more lines (Nos. 10–12) can be found between the $2\sigma_g$ and $2\sigma_u$ lines. Corresponding lines have been found in ESCA and represent other excited states of the N_2^+ molecule, reached by “shake-up” transitions. Unfortunately the higher excited states of N_2^+ are not well known, but there are doublet states at about 22.0 eV ($D^2\Pi_g$) and 23.6 eV ($C^2\Sigma_u^+$) above the ground states of neutral N_2 . An ionization of N_2 in the $2\sigma_u$ orbital leaves the ion in the $B^2\Sigma_u^+$ state which has the same symmetry as the C state and these two states are known to interact⁶. One can therefore expect an X-ray intensity of the $N1s \rightarrow C^2\Sigma_g^+$ transition due to configuration interaction. The ionization potential of N_2 for the vertical transition which

leaves the ion in the $C^2\Sigma_u^+$ state is expected to be 25.3 eV⁶. Because the $N1s$ ionization does not change the internuclear distance appreciably the same energy for the $C^2\Sigma_u^+$ state would be found in the X-ray spectrum. The transition to this state is identified as line No. 10 in our spectrum. Other contributions to the intensity of this line cannot be excluded, however. The remaining low energy satellites (Nos. 11 and 12) may be of similar origin to line No. 10.

Apart from the main X-ray lines and the low energy “shake-up” satellites five high energy satellite lines (Nos. 1–5) have been found. Four of these lines (Nos. 2–5) are quite weak while the one of highest energy (No. 1) is comparable in intensity to the main lines. It is known from X-ray absorption⁷, Auger^{1,8,9}, and ion-electron coincidence¹⁰ experiments that there is a highly excited, auto-ionizing level in N_2 , that corresponds to the excitation of an $N1s$ electron into the empty $1\pi_g$ orbital. The energy of this state is 400.8 eV above the ground state in neutral N_2 . The X-ray emission process which competes with the auto-ionization, would give rise to a spectral line at this energy as a result of an $N1s \rightarrow 1\pi_g$ “resonance transition” in neutral N_2 . The existence of such X-ray phenomena has been pointed out before^{1,11,12}.

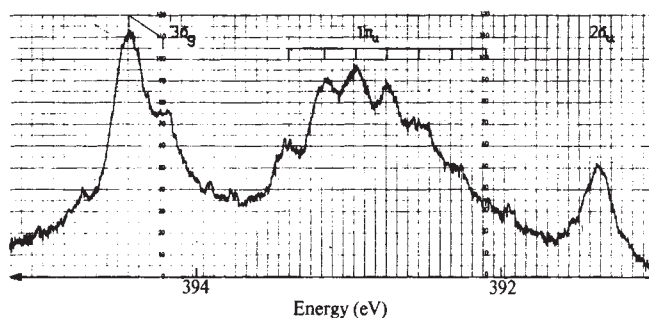


Fig. 2 Densitometer curve of the three main lines in Fig. 1. Fine structure due to molecular vibration is observed in the $3\sigma_g$ and $2\pi_u$ X-ray lines.

The satellite lines 2–5 are probably due to transition in doubly ionized or singly ionized excited molecules. The initial and final states of such transitions can be seen in the shake-up and Auger spectra, respectively, of ESCA. Shake-off begins at about 440 eV in the ESCA spectrum of N_2 (ref. 1) and the final states of the Auger transitions have energies around 43 eV and higher¹. This gives about the same X-ray transition energies as observed for the satellites 2–5.

Considering the high resolution that can now be obtained in molecular X-ray spectra it appears that this technique will be a useful complement to ESCA. In addition to the N_2 molecule discussed in this paper we have studied argon, CO, CO_2 , CS_2 and C_6H_6 . Some preliminary results on argon and CO have been published^{13,14} and we intend to discuss other aspects of this technique. For example, it is now possible to derive chemical shifts of core electron levels from X-ray and electron spectra, and the localization of valence orbitals on different atomic species within a molecule can be studied in the X-ray spectrum.

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¹ Siegbahn, K., Nordling, C., Johansson, G., Hedman, J., Hedén, P. F., Hamrin, K., Gelius, U., Bergmark, T., Werme, L. O., Manne, R., and Baer, Y., *ESCA Applied to Free Molecules* (North-Holland Publ. Co., Amsterdam-London, 1969).

- ² Turner, D. W., Baker, C., Baker, A. D., and Brundle, C. R., *Molecular Photoelectron Spectroscopy* (Wiley, London, 1970).
- ³ Siegbahn, K., Werme, L. O., Grennberg, B., Lindeberg, S., and Nordling, C., *Report No. UUIP-749*, Uppsala University, Institute of Physics, 1971.
- ⁴ Siegbahn, K., in *Electron Spectroscopy* (edit. by Shirley, D. A.) (North-Holland Publ. Co., Amsterdam 1972).
- ⁵ Dannhäuser, G., and Wiech, G., *Phys. Lett.*, **35A**, 208 (1971).
- ⁶ Gilmore, F. R., *J. Quant. Spectrosc. Radiat. Transfer*, **5**, 369 (1965).
- ⁷ Nakamura, M., Sasanuma, M., Sato, S., Watanabe, M., Yamashita, H., Iguchi, Y., Ejiri, A., Nakai, S., Yamaguchi, S., Sagawa, T., Nakai, Y., and Oshio, T., *Phys. Rev.*, **178**, 80 (1969).
- ⁸ Stalherm, D., Cleft, B., Hillig, H., and Mehlhorn, W., *Z. Naturforsch.*, **24a**, 1728 (1969).
- ⁹ Moddeman, W. E., Carlson, T. A., Krause, M. O., Pullen, B. P., Bull, W. E., and Schweitzer, G. K., *J. Chem. Phys.*, **55**, 2317 (1971).
- ¹⁰ Van Der Wiel, M. J., El-Sherbini, Th. M., and Brion, C. E., *Chem. Phys. Lett.*, **7**, 161 (1970).
- ¹¹ LaVilla, R. E., *J. Chem. Phys.*, **56**, 2345 (1972).
- ¹² Bonnelle, C., and Karnatak, R. C., *CR Acad. Sci.*, **B258**, 494 (1969).
- ¹³ Werme, L. O., Grennberg, B., Nordgren, J., Nordling, C., and Siegbahn, K., *Phys. Lett.*, **A41**, 113 (1972).
- ¹⁴ Siegbahn, K., Werme, L. O., Grennberg, B., Nordgren, J., and Nordling, C., *Phys. Lett.*, **A41**, 111 (1972).

High Strength Glass Fibre-Resin Composites

I have reported that the mean breaking stress of undamaged single fibres of borosilicate glass, tested in tension is consistent at 3.66 kN mm^{-2} over a wide range of fibre diameters, with little scatter¹. Commercial glass fibre strand, consisting of a large number of fibres aligned in parallel array, fractures at a mean breaking stress of 1.04 kN mm^{-2} ; and the value is determined by the individual fibre diameter in the strand. Single fibres taken from such strand have a mean breaking stress of 1.73 kN mm^{-2} . For both strand, and damaged fibres taken from the strand, the scatter in the results is large.

When glass fibres are embedded in a polymeric resin, the resin acts as an adhesive bonding the individual fibres together, and load transference is now possible between the discrete glass fibres. The strength of commercial strand in both epoxide and polyester resins is about 1.7 kN mm^{-2} and again the scatter is large².

Many attempts have been made to attain high glass strengths in composites. The methods employed are usually designed to prevent or reduce the amount of damage caused to the surface of the glass fibres during the production of the strand. The most successful way is to coat the glass with the resin during the production of the glass strand³, before the fibres come into contact with each other. This method, which can produce mean breaking stresses in excess of 2.8 kN mm^{-2} , is difficult to carry out commercially as the fibres are produced at drawing speeds in excess of $3,000 \text{ m min}^{-1}$.

I describe here a new method of achieving high glass strengths in resin composites. Commercial strand contains about 400 fibres each of diameter 0.013 mm , but by changing the drawing speed and the temperature of the fibre production process, strand can be produced over a range of fibre diameters. The fibre used in these experiments was produced in the laboratory with diameters ranging from 0.005 mm to 0.05 mm . The overall cross-sectional area of the strand was kept constant in each case at 0.05 mm^2 , the approximate area of commercial strand. This was achieved by varying the number of fibres in the strand from about 20 large fibres to 2,000 very fine fibres in the two extreme cases.

The standard 'Fibreglass' method⁴ was used to produce the glass fibre, in which glass is melted in an electrically heated platinum-rhodium crucible. Molten glass is drawn through nozzles in the base of the crucible and is wound onto a revolving drum at high speed.

After production, the strand was embedded in a series of polymeric resins and each strand was tested in tension, at a gauge length of 50 mm , at a strain rate of 25 mm min^{-1} , in an Instron Tensile Testing Machine, until fracture occurred. Forty samples were tested at each fibre diameter.

The results obtained for the mean breaking stress, based on the initial glass cross-sectional area, for three widely differing resin media are shown in Table 1, in which the scatter in the results is shown by the coefficient of variation. The values for the breaking stress of strand with no resin present, for commercial strand, and commercial strand in the three resins are included for comparison.

Table 1 Mean Breaking Stress and Scatter for Glass Fibres Embedded in Various Resins

Type of composite	Fibre diameter μm	Mean breaking stress GN m^{-2}	Coefficient of variation $\pm \%$
Strand only	6.10	1.064	15.8
	10.92	0.913	11.0
	12.95	0.899	20.8
	18.54	0.802	16.7
	27.94	0.733	21.1
	38.10	0.601	16.3
	51.05	0.581	31.9
Commercial strand	12.7	1.037	14.6
Strand in polystyrene resin	6.60	2.281	7.3
	12.95	1.998	9.9
	18.54	1.507	16.1
	25.65	1.244	14.9
	37.85	0.788	20.4
	52.32	0.588	23.0
Commercial strand in polystyrene resin	12.7	1.604	8.4
Strand in epoxide resin ('Araldite AY 105')	6.10	3.180	2.7
	8.38	3.076	3.5
	11.18	2.807	7.7
	12.95	2.634	10.5
	16.76	2.516	6.2
	24.89	1.797	22.0
	37.08	1.307	22.7
Commercial strand in epoxide resin	12.7	1.766	13.2
Strand in polyester resin ('Cellobond A 2622')	6.10	3.180	3.4
	10.92	3.069	3.8
	12.45	3.014	5.9
	18.54	2.710	7.6
	25.15	2.385	15.3
	36.83	1.977	23.0
	50.80	1.431	22.0
Commercial strand in polyester resin	12.7	1.749	14.9

For resin impregnated strand of constant glass cross-sectional area, the fibre diameter is of major importance. For the resins used there is an appreciable increase in the strand composite strengths as the fibre diameter is reduced.

The high strengths recorded for composites containing the thin fibres may be attributed to the fact that such fibres contain fewer external flaws and internal bubbles, and the total bonding area is much greater than that of a composite strand containing thick fibres. Further evidence of this is given by the fact that as the strengths increase, the scatter in the results falls appreciably.

For the resins used there is an increase in the strand composite strengths compared with those produced from commercial strand of a corresponding fibre diameter. This is probably due to the fact that the strand was embedded in the resin within minutes of production. In this series of tests no provision was made to protect the surface of the fibres by the application of a size or bonding agent, as is the usual practice in the production of commercial strand.

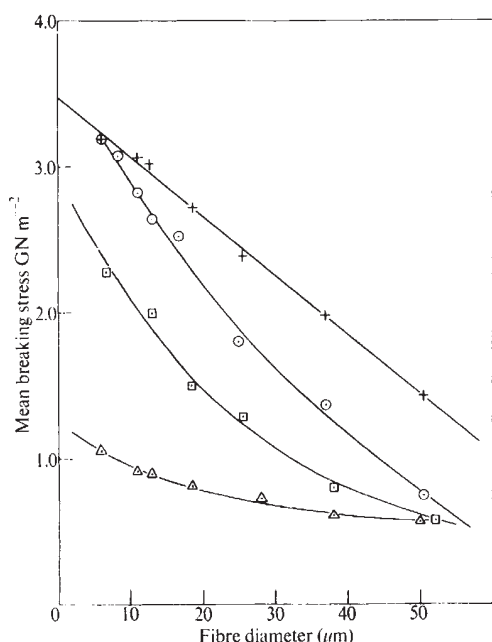


Fig. 1 Effect of fibre diameter on breaking stress in various resin matrices. Δ , Glass strand; $\square$, strand in polystyrene; $\circ$, strand in epoxide; $+$, strand in polyester.

The results indicate that if high strength composites are required, strand containing fibres of a diameter of about 0.005 mm should be used instead of the almost universally accepted fibre diameter of 0.013 mm. The final strength in the glass is in excess of 3.18 kN mm⁻², with little scatter. Extrapolation of the strength-diameter relationship for the polyester composite strand to infinitely fine fibres, as shown in Fig. 1, gives a mean breaking stress of just under 3.66 kN mm⁻², the strength of undamaged single fibres.

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¹ Thomas, W. F., *Phys. Chem. Glasses*, **1**, 4 (1960).

² Thomas, W. F., *Glass Technol.*, **13**, 17 (1971).

³ Gleeson, B., *Research Projects in Reinforced Plastics* (London Conference, 1968).

⁴ De Dani, A., *Chem. Ind.*, **18**, 482 (1955).

Alternative Statement of the Second Law of Thermodynamics

As usually stated, the second law of thermodynamics is asymmetric under time reversal, and is thus not compatible with a microscopic mechanics symmetric under time reversal. In its most popular form, the second law states that the entropy of a closed system tends to increase. Attempts to derive this from time-symmetric physical laws are self-defeating because any argument which leads to increasing entropy may be time reversed to produce an equally valid argument leading to decreasing entropy. Yet irreversibility is a fact of life. This is Loschmidt's paradox¹.

The problem has led to much discussion about the origin of the "arrow of time", some people believing that the laws of physics must be supplemented by an additional principle containing the seeds of irreversibility², others seeking some lack of temporal symmetry in the laws of physics themselves³; this problem has been discussed at length⁴⁻⁷.

I agree with the view that our observations do not themselves imply any temporal asymmetry, so that there is no conflict with symmetric laws. This was known to Boltzmann⁸ and has been discussed by other authors^{6,7}, yet it is not generally appreciated because we continue to state the second law in a form which is clearly asymmetric in time. Instead of shedding light on the traditional confusion among non-scientists regarding the apparent asymmetry of time, we have elevated it to the status of natural law. It is important to state the second law in such a way it is manifestly symmetric under time reversal. I propose that a proper generalization from our observations is: The entropy of a closed system tends to change monotonically with time.

A monotonic increase in entropy is certainly consistent with our observations, and so it is only necessary to establish that a monotonic decrease is also physically acceptable. If we were to observe a closed system whose entropy is decreasing monotonically it would not look like a film running backwards; we would not see familiar sequences of events in reverse order. This is because, by definition, to observe a closed system it is necessary to be within it. In fact the only closed system of which we have experience is that system of which the observable Universe is a part. We must ask how a monotonic decrease in entropy of a system appears to an observer who is a part of the system. Although familiar sequences of events may occur in reverse order, they will be observed in normal order by such an observer and will be physically acceptable to him, because an observer in such a system will "remember" the future rather than the past. The process of memory formation (or in general, of recording information), entails a net increase in the entropy of the system of which the observer (or recording machine) is a part. So in a closed system whose entropy changes monotonically, an observer remembers events which occur at times corresponding to lower entropy. The observations will be as acceptable in the case of monotonic decrease as in the case of monotonic increase. As an example of a system with monotonically decreasing entropy, imagine performing a complete time reversal on our Universe. This of course implies a reversal of our memory processes too, so that our observations would be utterly unchanged. Clearly, such a situation cannot be forbidden on thermodynamic grounds (though perhaps by weak interaction theory). If this simple point were to be made briefly in elementary text books on thermodynamics and statistical mechanics, much unnecessary heartache would be avoided.

It might be argued⁹ that the statement which I propose is equivalent to the usual statement on grounds of logical consistency. According to this argument, if the entropy of a given closed system increases with time, then so must that of any other closed system. With such a parallelism of entropy increase one may define the future as the direction of time in which entropy increases. The parallelism is argued by constructing a composite isolated system consisting of several subsystems isolated from each other, and if some of the subsystems are increasing in entropy while others are decreasing, one will not in general maintain a monotonic change in entropy for the composite system. Such an eventuality is physically acceptable, however, because any observer in this system can observe events only in his own subsystem. Thus there are no observational grounds for demanding a monotonic change in entropy for such composite systems, and hence no evidence for the parallelism of entropy increase. Presumably in stating the law one should exclude composite systems by demanding a monotonic change of entropy for systems which are closed and multiply-connected only; that is those which cannot be divided into two or more parts permanently isolated from each other. Reichenbach's principle of the parallelism of entropy increase⁶ refers not to systems which are permanently isolated from each other, but to hypothetical branch systems which are temporarily isolated from their surroundings. The increase in entropy of the branch systems during their period of isolation is a manifestation of the monotonic increase in entropy of the

Universe. It is precisely this parallelism in the behaviour of different parts of a system at different times that is at the heart of the second law.

How would one attempt to derive the second law, in the form proposed, from the laws of physics? One could imagine a simple generalization of the usual classical statistical argument in which one considers a system initially in a given macrostate and asks about the macrostate at some later time. If one counts all the phase space trajectories linking the initial macrostate to other macrostates, one is led to associate greater probability to those final macrostates with greater statistical weight. On the other hand, one could consider a system with a specified final macrostate, in which case a similar counting procedure implies that earlier macrostates must have greater statistical weight. This is hardly a satisfactory "proof" of the second law, and indeed there are those who would deny altogether the general validity of the second law, but would prefer to associate the monotonic increase in the entropy of our own system with non-thermodynamic features peculiar to it, such as cosmological expansion^{4,7}.

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¹ Loschmidt, J., *S.B. Akad. Wiss. Wein*, **73**, 139 (1876).

² Penrose, O., and Percival, I. C., *Proc. Phys. Soc.*, **79**, 606 (1962).

³ Landau, L. D., and Lifshitz, E. M., *Statistical Physics*, 28 (Pergamon Press, Oxford, 1969).

⁴ Landsberg, P. T., *Studium Generale*, **23**, 1108 (1970).

⁵ *Proc. Intern. Conf. Thermodynamics, Cardiff, 1970* (edit. by Landsberg, P. T.) (Butterworths, London, 1970).

⁶ Reichenbach, H., *The Direction of Time* (Univ. of California Press, Berkeley, 1956).

⁷ *The Nature of Time* (edit. by Gold, T.) (Cornell Univ. Press, 1967).

⁸ Boltzmann, L., *Lectures on Gas Theory*, section 90 (Univ. of California Press, 1964).

⁹ Landsberg, P. T., *Thermodynamics*, 82 (Interscience, New York, 1961).

Consequences of Cycles in East African Climate

Western and Van Praet¹ have convincingly suggested that losses of yellow fever-trees in the Maasi Ambolesi are not due to over-population by cattle or elephants but to a climatic change causing a shift in the salt table. They assume that the change is part of a cycle, though of a much smaller range than has occurred in the past 10,000 yr. Perhaps inadvertently, they seem to suggest that the cycle producing the present vegetation change lasts about a century. Much shorter cycles than this may, however, be usual in the region, as evidence from further south suggests. It is important that this should be appreciated because, as the authors state, investment by governments on developments to accommodate tourists may be wasted if the climate is wrongly forecast.

Western and Van Praet cite evidence for synchronous changes in levels of lakes over a large area of East Africa, especially in those lakes that have no outlet to the sea; Rukwa is one of those lakes² and evidence from Lake Rukwa may be appropriate in the Maasi Ambolesi.

Rainfall or lake levels of Lake Rukwa, going back far enough, have not been recorded, so I have to rely on travellers' tales and inferences³. My information refers to rather few separate years but covers a century discontinuously. A dry period or a wet period, as indicated by lake levels, lasts several years. For example, Lake Rukwa has been very full from 1963 until

today, as it was for years around 1937. Between these two wet periods, the larger northern part of the lake has been so dry that in 1954 we could drive loaded 3-ton lorries across it. In earlier dry periods, when there were no mechanical vehicles to traverse the 30 miles of alkaline dust, the narrower parts of the lake bed could be crossed dry shod or ankle deep. In wet periods, 1,500 mile² or more of the northern lake was open to fishing from canoes. Table 1 shows reasonably well authenticated reports suggesting three or four cycles in a century.

Table 1 Available Information on State of Lake Rukwa, over 100 yr

Lake Rukwa	State	Author or authority ³
1873	Dryish	Livingstone's last journey
1880-2	Very high	Joseph Thomson; Emil Kaiser
1892	Dry	Sir Harry Johnstone; Cross; Wallace
1904	High	Meyer
1920	Dry	Mateo
1933-42	High	Michelmores; Swynnerton; Bredo ^{4,5}
1954	Quite dry	Gunn ⁵
1963-	Very high	Du Plessis; Kühne ⁵

I found that upsurges of red locust populations in the Rukwa Valley have been associated with low levels of the lake³. Symmons⁴ went further and showed a close relation between lake levels and cumulative deviation from average rainfall and a good correlation between locust numbers and previous rainfall; these have been used for forecasting locust numbers in Rukwa more than a year ahead⁶. It may have the salt-table mechanism proposed by Western and Van Praet and the cumulative deviation from average rainfall may also apply to both cases. If it does, sound planning for the Maasi Ambolesi may be facilitated.

On this very large scale, another consequence of climatic cycles is worth recording. During both recent periods of high level in Lake Rukwa, around 1937 and 1967, red locust breeding occurred on a threatening scale in Mocambique; such breeding has never been recorded there in years when Rukwa lake levels were low. Here, too, forecasting is worth attempting and perhaps also in other related matters in East Africa.

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¹ Western, D., and van Praet, C., *Nature*, **241**, 104 (1973).

² Butzer, K. W., Isaac, G. L., Richardson, J. L., and Wasbourn-Kamau, C., *Science*, **175**, 1069 (1972).

³ Gunn, D. L., *Tanganyika Notes and Records*, **42**, 1 (1956).

⁴ Symmons, P. M., *Bull. Ent. Res.*, **50**, 507 (1959).

⁵ Annual Reports of the International Red Locust Control Service, Abercorn, Northern Rhodesia (Mbala, Zambia).

⁶ Gunn, D. L. and Symmons, P. M., *Nature*, **184**, 1425 (1959).

BIOLOGICAL SCIENCES

Movement of Sodium Ions Associated with the Nerve Impulse

HODGKIN AND HUXLEY¹ calculated the extra sodium fluxes in the squid giant axon resulting from the passage of nerve impulses assuming that the time course of the observed currents represented the time course of a change in permeability. The net flux was in rough agreement with experimental data at room temperature but there was more exchange in the axon than in computed predictions. As the calculated fluxes increase by a factor of three when the temperature is reduced 10° it seemed appropriate to test the effect of temperature on the sodium fluxes.

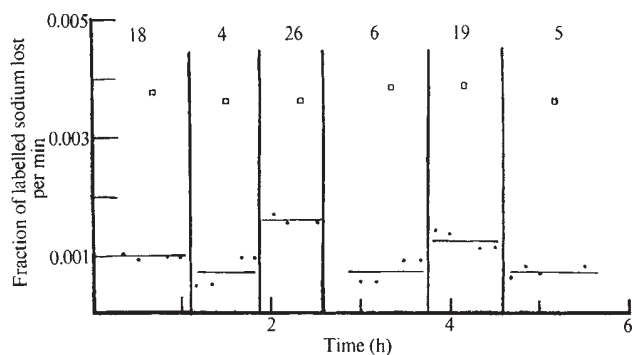


Fig. 1 The effect of temperature on the efflux of sodium from the resting (●) and stimulated (□) squid giant axon. The axon was loaded with radioactive sodium 2 h previous to this record by stimulating in radioactive seawater for 10 min at 150/s. During the stimulated collecting periods the axon was stimulated for the first 5 min of the 10 min period. Temperature is given in the numbers above each section of the experiment. 10 μ M ouabain was present in the sea water throughout the experiment.

For influx experiments pairs of axons were dissected from *Loligo forbesi* and placed, uncleaned, in a chamber with 1–2 ml. of seawater made radioactive with ^{22}Na . The nerves were allowed to soak for 5–10 min and then one nerve was stimulated 50 times per second for 10–30 min. The nerve impulses were continuously monitored with external electrodes and an oscilloscope. A sample of the radioactive seawater was taken, the excitability of the control nerve checked, and then the ends of the axons were cleaned and the axoplasm extruded², weighed and counted in a well scintillation gamma counter. The difference between the two axons was taken as the extra influx due to activity. The experiments were performed either at room temperature (20–22° C) or in a constant temperature room (6–7° C). The results are given in Table 1. The observed extra influx at low temperature is actually smaller than at high temperature instead of much larger as predicted by Hodgkin and Huxley. The extra influx found at room temperature is similar to other observations in squid axons³.

Table 1 Extra Influx of Sodium Associated with Nerve Impulses Expressed in $\text{pmol cm}^{-2}\text{-impulse} \pm \text{Standard Error}$.

	6–7° C	20–22° C	Q_{10}
Observed values	3.4 ± 0.8 (5)	5.9 ± 1.1 (6)	1.5
Predicted value for membrane action potentials, Hodgkin and Huxley ¹ Table 5	19.3	5.0*	1/3

* Computed for 18.5° C.

Number of experiments in parentheses.

In a few preliminary experiments the efflux of sodium ions was measured by a method similar to that of Hodgkin and Keynes⁸. The axon was cleaned, loaded by stimulating in radioactive seawater and placed in a water-jacketed tube. The amount of tracer leaving the nerve per unit time was measured by collecting seawater which flowed continuously over the nerve. A typical experiment is shown in Fig. 1 where the fraction of the radioactive isotope leaving the axon per minute is plotted against time. One can easily see that the rate of efflux does not increase threefold for a 10° C reduction of the temperature.

Although there are no published experiments directly measuring the stimulated fluxes as a function of temperature, there is indirect evidence which supports the present findings. In an experiment at 7.5° C, using an indirect method, Moore and Adelman⁴ found only 1.5 $\text{pmol cm}^{-2}\text{-impulse}$ for the net influx whereas the theory of Hodgkin and Huxley predicts several times this much. In the data given in Table 5 of Hodgkin and Huxley no change had been seen in the net

influx of sodium over a range of 8° C although a Q_{10} of 1/3 predicts that more than twice as much sodium should enter at the lower temperature. In the rabbit vagus nerve there is evidence that the total amount of sodium gained by the fibre per impulse is largely independent of temperature⁵.

These data seem to rule out any model of the nerve membrane which accounts for the current by a simple change in permeability. At low temperatures the nerve impulse has a much longer duration, the time course of the voltage clamp currents are greatly prolonged, and so the predicted ionic fluxes are considerably larger. This is true whether the permeability change is brought about by an alignment of particles¹ or the opening of a pore⁶. This suggests that a new way of thinking about the observed currents is necessary.

I have recently proposed an explanation of the ionic currents based on a consideration of space charge limitation⁷. In this model the amount of sodium which moves during the nerve impulse is limited to the amount in the membrane before the impulse. The passage of an impulse leaves the membrane depleted of sodium which makes the nerve refractory. As a first approximation one would not expect the content of the membrane phase to vary dramatically with temperature. It was this consideration which led to these flux measurements.

My explanation predicts that the membrane sodium content, and thus the extra sodium influx, should increase with increasing temperature. The ions enter the lipid phase rather than the vacuum of a thermionic diode. At higher temperatures more ions will be able to overcome the interface potential energy barrier (analogous to the work function in a metal) and enter the lipid phase of the membrane. From the data presented here one can calculate a potential barrier of 0.28 eV corresponding to the observed Q_{10} of 1.5. It is interesting to note that in *Sepia* axons the resting sodium influx increases with a temperature coefficient of about this size⁸ as does the maximum sodium conductance ($\bar{g}_{\text{Na}}$) in the squid axon⁹ as one might predict because they also should vary with the number of current carriers in the membrane phase.

How, then, are the prolonged voltage clamp currents at low temperatures explained in terms of the space charge limited model? As indicated previously⁷ the kinetics of a space charge limited diode are temperature dependent because at higher temperature the ions have more thermal kinetic energy and enter the membrane with a higher average initial velocity. Because the ions enter with a non-zero initial velocity they tend to accumulate inside the membrane and form a potential maximum. (In discussions of vacuum diodes this is a potential minimum because electrons with a negative charge carry the current instead of positively charged ions) and is referred to as a "virtual cathode"¹⁰.

The virtual cathode behaves as a source of charge carriers. At high temperatures the ions enter with a higher initial velocity, the potential maximum is closer to the far side of the membrane and thus the distance travelled by the ions during the voltage clamp pulse is shorter. This means that the transit time is less and the currents change more rapidly. At low temperatures the ions travel further in the membrane. As shown in Fig. 2, the same number of ions can produce current for a longer time by travelling a longer distance. Thus the flux, as measured by radioactive tracers, is not equal to the time integral of the current observed in the external circuit. This is different from the situation found in metals or electrolyte solutions because in both cases the spatial distribution of charge carriers is uniform and does not vary with time. The difficulties in applying Kirchhoff's rules to this system also arise from this difference in charge distribution. At first it may seem somewhat surprising to suggest that a relatively large amount of free charge is in the lipid phase. However, it has been quite convincingly shown that substances commonly considered insulators can carry large currents if they have been provided with suitable,

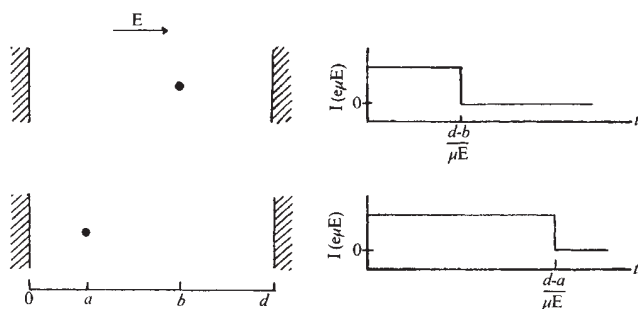


Fig. 2 The current associated with a single positive ion moving through a dense medium. The electric field is applied at $t=0$ with the ions (●) starting at the positions indicated. The current, I , measured in the external circuit for one ion is the charge on the ion, e , times its drift velocity (the mobility, μ , times the field strength, E). The current persists as long as the ion is between the electrodes, that is, between the two aqueous phases. The transit time is the distance travelled divided by the drift velocity.

low work function, electrodes^{11,12} The work function of a metal can be altered by dipoles or charges at its interface. Presumably this also occurs at the cell's aqueous-lipid interface.

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- ¹ Hodgkin, A. L., and Huxley, A. F., *J. Physiol.*, **117**, 500 (1952).
- ² Hodgkin, A. L., and Keynes, R. D., *J. Physiol.*, **138**, 253 (1957).
- ³ Shaw, T. I., *J. Physiol.*, **182**, 209 (1966).
- ⁴ Moore, J. W., and Adelman, W. J., *J. Gen. Physiol.*, **45**, 77 (1961).
- ⁵ den Hertog, A., and Ritchie, J. M., *J. Physiol.*, **204**, 523 (1969).
- ⁶ Hille, B., *Prog. Biophys. and Mol. Biol.*, **21**, 3 (1970).
- ⁷ Landowne, D., *J. Physiol.*, **222**, 46P (1972).
- ⁸ Hodgkin, A. L., and Keynes, R. D., *J. Physiol.*, **128**, 28 (1955).
- ⁹ Moore, J. W., *Fed. Proc.*, **17**, 113 (1958).
- ¹⁰ Langmuir, I., and Compton, K. T., *Rev. Mod. Phys.*, **3**, 191 (1931).
- ¹¹ Mott, N. F., and Gurney, R. W., *Electronic Processes in Ionic Crystals*, 168 (Oxford University Press, 1940).
- ¹² Smith, R. W., and Rose, A., *Phys. Rev.*, **97**, 1531 (1955).

Currents Related to Movement of the Gating Particles of the Sodium Channels

"... It seems difficult to escape the conclusion that the changes in ionic permeability depend on the movement of some component of the membrane which behaves as though it had a large charge or dipole moment". With these words Hodgkin and Huxley predicted the existence of gating currents: charge movement associated with molecular rearrangements that attend the opening and closing of the ionic channels in response to changes in the membrane field. The polarity of gating current of the sodium channels can be easily predicted: following a positive step change of membrane voltage, positively charged gating particles would move outward through the membrane field from closed to open position (or negatively charged particles would move inward), yielding an outward current. On repolarization after a voltage step that opened the channels, gating current would be inward, as particles moved from open to closed position. Hodgkin and Huxley were unable to

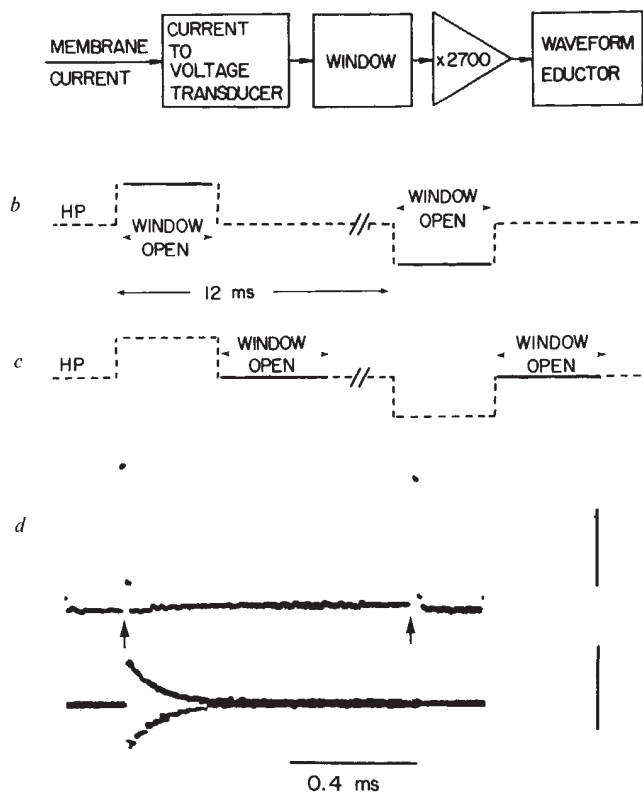


Fig. 1 a, b, c, See text. d, Lower trace: current resulting from a positive and a negative voltage pulse applied to a passive RC circuit. The calibration bar is equivalent to $2.5 \text{ pA } \mu\text{m}^{-2}$. Upper trace: averaged and summed current for 4,000 positive and 4,000 negative pulses. The calibration bar is equivalent to $0.05 \text{ pA } \mu\text{m}^{-2}$. The window opened $30 \mu\text{s}$ after the beginning of the pulse (left arrow) and closed at the right arrow.

observe gating currents experimentally, and concluded that the density of ionic channels in the membrane must be low. A later attempt by Chandler and Meves² to detect such currents was also unsuccessful, and they estimated that there are less than 100 sodium channels μm^{-2} , a prediction that has been borne out by later estimates of sodium channel density^{3,4}. We report here that by use of signal averaging techniques, we have observed small transient currents which we believe are the gating currents of the sodium channels.

Our experiments were performed on isolated squid giant axons, which were internally perfused and voltage clamped. A major technical problem is that the expected gating currents should be obscured by the relatively enormous capacitive and ionic currents. To minimize ionic currents we perfused the interiors of the fibres with a solution containing Cs^+ ion, which is impermeant, in place of K^+ ion, and we replaced external sodium with the impermeant ion Tris. In many experiments the external medium also contained $2 \times 10^{-7} \text{ M}$ tetrodotoxin to suppress ionic movement through sodium channels. There remains nonetheless a substantial ionic current (leakage) on which the gating currents are superimposed. The leakage current was large enough to saturate our amplifiers, but fortunately it is time invariant, and we eliminated it by feeding an offsetting current into the current to voltage transducer (see below).

Imperfections in the membrane dielectric of the squid giant axon (a small portion of which may arise from gating particle movement) cause a slow tail of capacitive current which is large compared with the anticipated gating currents. Most of this tail current was eliminated by algebraically summing the current from exactly matched pulses of opposite sign. The remaining current is not symmetrical for pulses of opposite sign, and may be gating current. In practice positive and

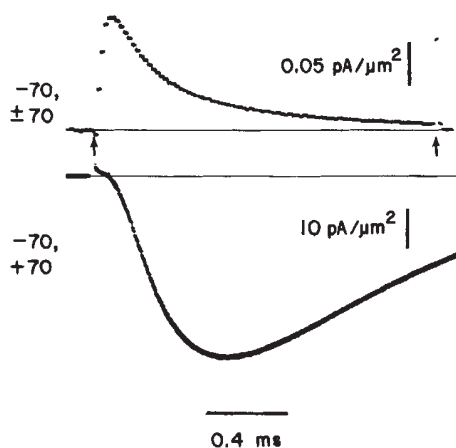


Fig. 2 Sodium current (lower trace) and presumed gating current (upper trace: procedure of Fig. 1b) from the same axon. For the lower trace the axon was in artificial seawater and internally perfused with 275 mM KF+400 mM sucrose, at 3.5° C. Upper trace: averaged current for pulses of ± 70 mV from a holding potential of -70 mV. The axon was in Tris seawater, internally perfused with 550 mM CsF, at 3.5° C. The window opened 20 μ s after the beginning of the pulse (left arrow) and closed at the arrow on the right. Tris seawater was K-free.

negative pulses were alternated at 12 ms intervals, as shown in Fig. 1b and c. To prevent saturation of our amplifiers by the very large signal representing the early part of the capacitive current transient, we devised a "window" (Fig. 1a) which shut out the first 10–30 μ s of the signal following a voltage step, as illustrated in Fig. 1b and c. The signal passing through the window was amplified and fed to a Princeton Applied Research Waveform Eductor, which performed the dual function of algebraically summing the currents and averaging them. Each of our records is the average of current from several thousand pulses of each polarity. The apparatus was tested by applying alternating pulses to a passive RC circuit designed to give tail currents of about the same amplitude and time course as those recorded from the membrane. The results of a test are shown in Fig. 1d. The lower traces show the current for a positive and a negative pulse, with the first 30 μ s after the beginning of pulses excluded by the window. The upper trace shows the averaged sum of current for 4,000 positive and 4,000 negative pulses. The first point after the opening of the window (representing 10 μ s) is seriously misplaced and the next bit is slightly so, but after these the current sum is zero. Thus nothing resembling gating currents are observed when pulses are applied to a circuit composed of ordinary capacitors, which shows that the apparatus functions well and introduces minimal artefact.

The upper trace in Fig. 2 shows what we think is predominantly gating current of the sodium channels. The trace is the algebraically summed, average current for 2,000 positive and 2,000 negative pulses of 70 mV amplitude, from a holding potential of -70 mV. The window opened at the arrow on the right, 20 μ s after the beginning of the pulse, and remained open until just before the beginning of the step back to the holding potential (procedure of Fig. 1b). Each point on the trace gives the average current during a 20 μ s interval. The current rises for 80 μ s (four points) to a peak amplitude of 0.13 pA μ m $^{-2}$ and then declines toward a steady level set by the leakage current. This level is approximated in the figure by the thin line. The transient is outward in direction, and its time course is rapid in comparison to the sodium current (lower trace, Fig. 2) recorded from the same axon in conventional solutions (artificial seawater outside, KF inside). The maximum amplitude of the sodium current is about 300 times that of the presumed gating current.

The average current shown in Fig. 2 is almost certainly the sum of inward current during the negative pulses and outward current during the positive pulses. We think that the rising

phase is due to the rapid decay of a negative (inward) current, and that the outward component, seen alone, would rise instantaneously and decay monotonically. In theory if the holding potential were more positive, more of the gating particles would be in the open position at the holding potential, and the inward current during the negative pulses would be larger than for a more negative holding potential. Fig. 3a, b, and c shows the results of an experiment to test this point. Summed and averaged current is illustrated for three holding potentials, and the thin lines give the current level approached by the end of the trace. For a holding potential of -50 mV there is a conspicuous transient current that is inward relative to the steady level, followed by a small outward current; while at -70 mV there is almost no inward current and a larger outward current, just as expected. At a holding potential of -100 mV (Fig. 3c) the rising phase is almost absent, again as expected, for in this case almost all of the gating particles are in closed position at the holding potential.

In the procedure just described, the dominant charge movement for steps from a holding potential of -70 mV occurs during the positive pulse and is outward. At the end of the positive pulse there should in theory be inward charge movement, as gating particles move back from open to closed

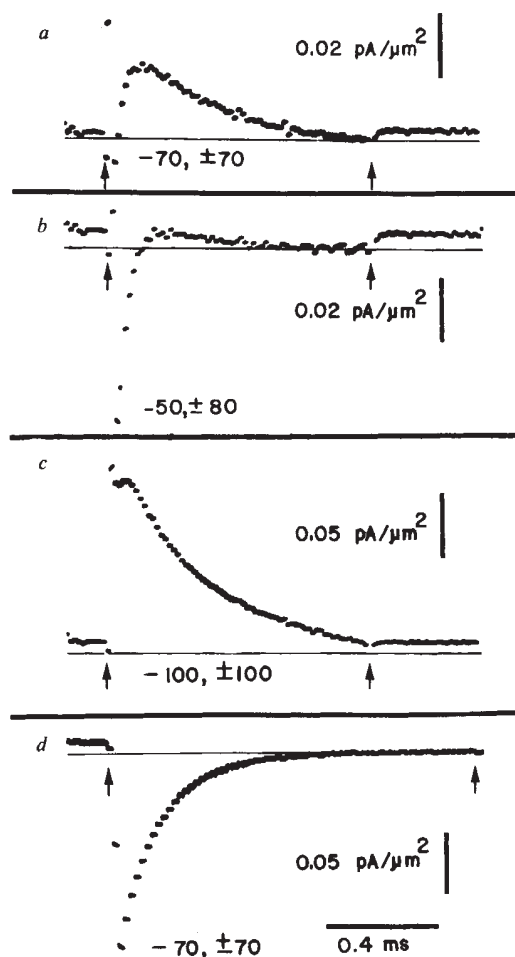


Fig. 3 a, b, c, Presumed gating currents during pulses of the indicated amplitudes ($\pm y$), from the indicated holding potentials ($-x$) (procedure of Fig. 1b). The window opened 20 μ s after the beginning of the pulses. Tris seawater + 2×10^{-7} M tetrodotoxin, internally perfused with 550 mM CsF, at 2° C. d, Gating currents at the end of pulses of 70 mV amplitude from a holding potential of -70 mV (procedure of Fig. 1c). The window opened 20 μ s after the end of the pulses. Tris seawater + 2×10^{-7} M tetrodotoxin, internally perfused with 275 mM CsF + 138 mM KF + 200 mM sucrose, at 2° C. a, b, c, from one axon, d, from another. Arrows indicate opening and closing of the window. Tris seawater was K-free.

position. Charge movement during the negative pulse is relatively small, and the outward current expected at the end of the negative pulse should be overshadowed by the relatively large inward movement at the end of the positive pulse. When the window is opened after the pulses (procedure of Fig. 1c) an inward current is in fact observed (Fig. 3d), primarily reflecting, we think, the closing of gates after the positive pulse.

In theory the sum of gating charge movement during steps of, for example, ± 70 mV should be equal but opposite in sign to the sum of movement after the steps, as particles displaced by the pulses return to positions appropriate to the holding potential. In two experiments to test this, the movement during the pulses differed from that after by only 2% in one experiment and 8% in the other. This provides strong evidence that the observed currents are due to charge movement within the membrane, for it is highly improbable that ionic movement through the membrane channels during the pulses would exactly equal in magnitude ionic movement after them. Additional strong evidence that the observed currents are not ionic movements through the sodium channels is the fact that they are unaffected by tetrodotoxin.

The evidence that it is gating charge movement is as follows.

(i) Experiments on axons not poisoned with tetrodotoxin show that the current patterns illustrated above are obtained only from axons that have a normally functioning sodium permeability, both before and after the averaging procedure. Some axons give a different pattern, an inward current in all circumstances, but this pattern is always correlated with a high leakage current and with the absence of normal sodium permeability on return to artificial sea water outside and KF inside. (ii) The charge movement has a rapid time course that is compatible with changes leading to the opening of the activation gates of the sodium channels. The time course of the charge movement is too rapid for it to be readily associated with inactivation of the sodium permeability or activation of the potassium permeability, which are relatively slow processes. Also, because they are slow, gating current associated with these processes would be relatively small (unless the total charge movement is unexpectedly large) and their contribution to the observed current is thus probably minor. The absence of a tetrodotoxin effect on presumed sodium channel gating currents may seem surprising, but is not unexpected, for tetrodotoxin has no effect on g_{Na} kinetics^{5,6}. Our evidence seems to confirm that tetrodotoxin blocks the sodium channels without altering the operation of their gates. (iii) The dependence of the amplitude and shape of these currents on holding potential and pulse size agrees qualitatively with the behaviour expected of particles responsible for the activation of the sodium permeability. (iv) The net charge movement is consistent with estimates of Na channel density. From the dependence of sodium permeability on voltage it has been estimated that the gating particles that activate each Na channel have a net charge equivalent to that of six electrons¹. For a holding potential of -100 mV and pulses of ± 100 mV, the net charge movement in our experiments is about 300 electronic charges/ μm^2 . Dividing this figure by six electronic charges/channel, one obtains 50 channels/ μm^2 , in reasonable agreement with estimates derived from studies of tetrodotoxin binding to other axonal membrane^{3,4}.

Recently, Schneider and Chandler⁷ have successfully recorded intramembrane charge movement in muscle fibres which may be related to excitation-contraction coupling. The charge movement they observed is somewhat larger and slower by almost two orders of magnitude than that reported here, altogether too slow to be related to gating of the action potential permeabilities.

Our results support the hypothesis that permeability changes are brought about by the movement of charged particles or dipoles within the membrane in response to changes in the membrane potential.

We thank Dr E. Rojas for first interesting us in attempting to measure gating currents, and for his collaboration in early

attempts to do so, and Dr Clara Franzini-Armstrong for dissecting many of the axons.

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¹ Hodgkin, A. L., and Huxley, A. F., *J. Physiol.*, **117**, 500 (1952).

² Chandler, W. K., and Meves, H., *J. Physiol.*, **180**, 788 (1965).

³ Moore, J. W., Narahashi, T., and Shaw, T., *J. Physiol.*, **188**, 99 (1965).

⁴ Keynes, R. D., Ritchie, J. M., and Rojas, E., *J. Physiol.*, **213**, 235 (1971).

⁵ Hille, B., *Nature*, **210**, 1220 (1966).

⁶ Takata, M., Moore, J. W., Kao, C. Y., and Fuhrman, F. A., *J. Gen. Physiol.*, **49**, 977 (1966).

⁷ Schneider, M., and Chandler, W. K., *Nature* (in the press).

Contractile Effects of a Calcium Ionophore

THE contractile state of muscle is controlled through variations of the intracellular concentration of calcium ion¹⁻³. In different types of muscle, Ca^{2+} transients inside the fibres are sustained to various degrees by calcium movements to and from intracellular stores, such as the sarcoplasmic reticulum (SR). In skeletal muscle, the activity of SR is sufficient to account for release and uptake of intracellular calcium, fulfilling concentration and time requirements for a single twitch. But it is not as well developed in cardiac and even less so in smooth muscle.

The role of calcium in excitation-contraction coupling has been explained and verified with a variety of physiological and biochemical techniques, involving simple contractile systems, subcellular fractions, and purified proteins. No satisfactory method for a specific interference with this control system in whole muscle, however, has yet been discovered. Caffeine⁴ and Ryanodine⁵, two agents whose contractile effects have been attributed to alteration of calcium transients, are only partially effective on isolated SR, and their molecular mechanism of action is still unknown.

We have found that the calcium ionophore X-537A, at μM concentrations, causes rapid release of accumulated calcium from SR vesicles^{6,7} and has marked contractile effects in isolated preparations of skeletal, cardiac and vascular smooth muscle. X-537A is an antibiotic obtained from an unidentified streptomycete⁸ whose structure⁹ is given in Fig. 1. The antibiotic is known to bind divalent cations; its barium complex was studied by X-ray diffraction¹⁰, and shown to be made of two antibiotic molecules encircling one barium ion and one water molecule, stabilized by coordination and hydrogen bonding. The complex has a spherical shape, enclosing the ion in a hydrophilic pocket, while the exterior is non-polar and lipophilic, and for this reason, X-537A increases the

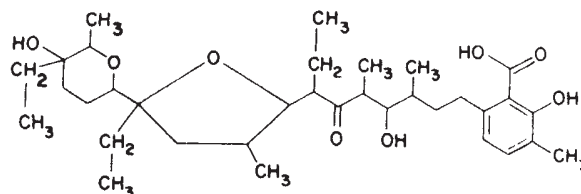
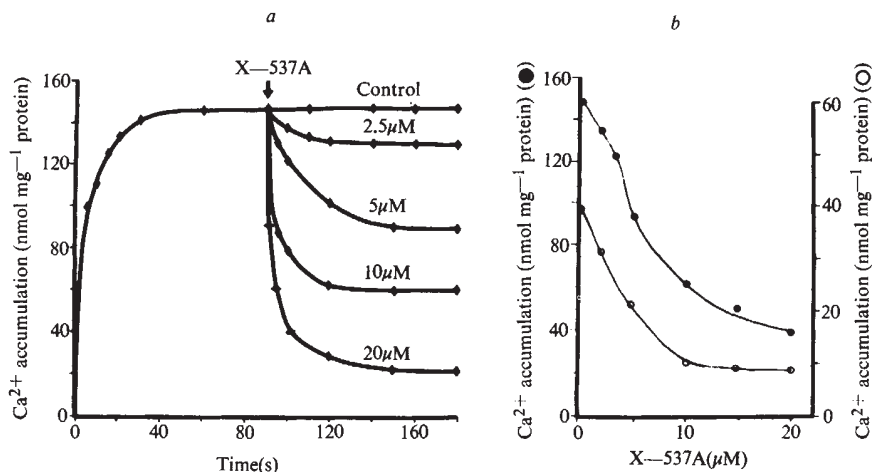


Fig. 1 Structure of X-537A.

Fig. 2 *a*, Calcium accumulation by SR vesicles, followed by X-537A induced release. *b*, Steady state levels of calcium accumulation by skeletal (●) and cardiac (○) SR, in the presence of different concentrations of X-537A. SR was prepared and calcium accumulation was measured at 25° C in the presence of 20 mM histidine, pH 7.0, 80 mM KCl, 5 μ M MgCl₂, 5×10^{-5} M ⁴⁵Ca-CaCl₂ and 350–400 μ g SR protein ml⁻¹. The reaction was started by the addition of 2.5 mM ATP, and stopped by 'Millipore' filtration¹².



permeability of artificial and natural membranes to divalent cations¹¹.

Addition of the ionophore to SR vesicles previously filled with calcium through the action of the membrane pump results in rapid release of the accumulated calcium. An identical concentration dependence of this effect is obtained in both skeletal and cardiac SR (Fig. 2). These concentrations produce increased resting tension and contracture in both twitching and quiescent diaphragm strips (Fig. 3). The effect is maximal in approximately 10 min and therefore its onset is slower than observed in isolated SR vesicles, probably due to slow penetration of the ionophore into the muscle fibres.

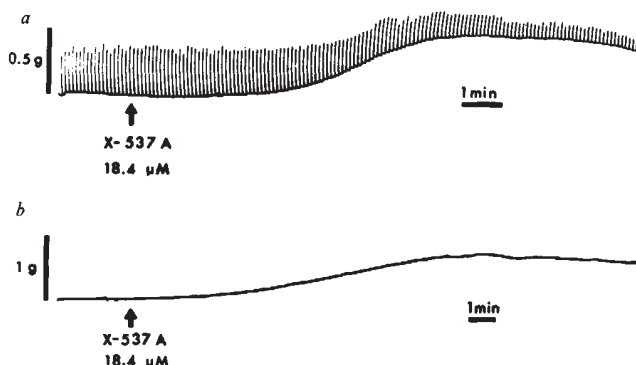


Fig. 3 Isometric tension of isolated strips of rat diaphragm. Bathing solution, 118 mM NaCl, 4.75 mM KCl, 2.54 mM CaCl₂, 1.19 mM MgSO₄, 1.19 mM KH₂PO₄, 12.5 mM NaHCO₃, 5.56 mM glucose. Gassing mixture 95% O₂-5% CO₂ at 37° C. Muscle length was adjusted to obtain maximal tension development. *a*, Muscle stimulated directly with a suprathreshold current, of 3 ms pulse duration; *b*, muscle was not stimulated.

Time resolution of single contractile cycles (Fig. 4) shows that while the resting tension is increased and the twitch tension decreased by the ionophore, the times of peak tension development and decay are unchanged.

Considering present knowledge on the regulatory role of calcium on the contractile state of myofibrils, one expects that a calcium ionophore, entering a muscle fibre, would induce a state of contracture by altering intracellular calcium gradients and interfering with physiological modulations of calcium concentrations. This in fact was observed in skeletal muscle preparations.

The ionophore was effective both in twitching and quiescent muscles, so the observed contractile effect was therefore not dependent on an alteration of the membrane action potential.

Because X-537A is active in SR vesicles and on whole muscle preparations within the same range of concentrations, we might speculate that the calcium sequestering ability of SR

is also impaired by the ionophore in whole muscles, and is directly involved in the development of contracture induced by the ionophore. On the other hand, this effect may also be produced by an increased permeability to calcium in the surface membranes of the muscle fibres.

Our experiments indicate that resting and twitch tensions, but not the times for peak tension development and decay, may be altered by interfering with transmembrane calcium gradients and by raising the steady state concentrations of intracellular calcium ion.

Contrary to experiments with skeletal muscle, those with cardiac preparations yielded more complex results. On electrically driven rabbit heart left atria and guinea-pig ventricular strips, low concentrations of X-537A (2.5–5.0 μ M) produced a positive inotropic effect (Fig. 5), characterized by

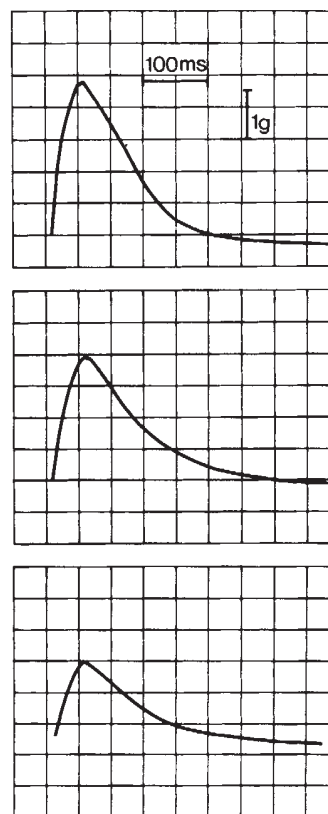


Fig. 4 Oscilloscopic traces of single twitches of rat diaphragm strips. Experimental conditions as in Fig. 3, except bath temperature was 25° C. From top to bottom: before, 3 and 6 min after addition of X-537A (20 μ M).

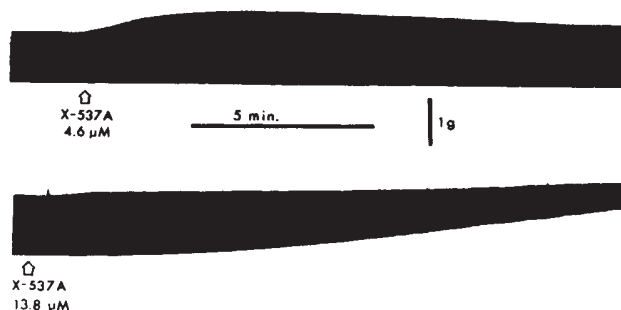


Fig. 5 Isometric tension of isolated rabbit atrium¹³. Bath solution as in Fig. 3. The muscle was stimulated with square wave stimuli of 5 ms duration, at 3 times threshold current, at a frequency of 2.0 Hz.

increased twitch tension, and no change either in times of peak tension development and decay or in resting tension. The inotropic effect was transient and could not be repeated by further additions of ionophore. After its occurrence, the cardiac preparations were not responsive to catecholamine releasing agents such as tyramine, but were still responsive to isoproterenol and norepinephrine. The positive inotropic effect of X-537A was not obtained after beta-adrenergic blockade with propranolol, or depletion of catecholamines by pretreatment of the animals with reserpine.

All of this evidence indicates that, in cardiac muscle, the positive inotropic effect at low concentrations (2.5–5.0 μM) of X-537A is due to release of endogenous catecholamines. The release may be related to the ability of X-537A to complex and transfer catecholamines across organic phases¹¹.

On the other hand, in cardiac preparations (Fig. 5), the ionophore at concentrations (5–20 μM) equal to those effective in skeletal muscle and in SR vesicles, produces increased rest tension and contracture. This is best observed in the presence of beta-adrenergic blockade, when the transient inotropic effect is absent and the effect of the ionophore is analogous to that observed in skeletal muscle. In this way, the catecholamines and calcium mediated effects can be differentiated.

As reported by Pressman¹¹, in smooth muscle (rabbit aortic strips), X-537A produces a transient contraction followed by a slight elevation of resting tone. We found that in the absence of endogenous catecholamines (that is reserpine) the transient contractile tension response to the ionophore was attenuated, but elevation of resting tension persisted.

The calcium ionophore properties of X-537A are reflected in its contractile effects on isolated muscle preparations. The ionophore, at concentrations inducing total release of accumulated calcium from SR vesicles, produces contracture or increased resting tension in skeletal (3–6 g tension/100 mg wet weight), cardiac (2–3 g tension/100 mg wet weight) and smooth (0.4–0.6 g tension/100 mg wet weight) muscles.

In addition, very low concentrations (2.5 μM) of X-536A induce a positive inotropic effect in cardiac preparations and the occurrence of contraction in smooth muscle. These transient effects are mediated by release of endogenous catecholamines, and are not obtained in skeletal muscle.

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- ¹ Ebashi, S., *Progr. Theoret. Phys., Suppl.*, **17**, 35 (1961).
- ² Hasselback, W., *Prog. Biophys. Biophys. Chem.*, **14**, 169 (1964).
- ³ Weber, A., *Current Topics in Bioenergetics* (edit. by Samadi, D. R.), **1**, 203 (Academic Press, New York, 1966).
- ⁴ Weber, A., and Herz, R., *J. Gen. Physiol.*, **52**, 760 (1968).
- ⁵ Jenden, D. J., and Fairhurst, A. S., *Pharmacol. Rev.*, **21**, 1 (1969).
- ⁶ Scarpa, A., and Inesi, G., *FEBS Lett.*, **22**, 273 (1972).
- ⁷ Entman, M. L., Gillette, P. C., Wallick, E. T., Pressman, B. C., and Schwartz, A., *Biochem. Biophys. Res. Comm.*, **48**, 847 (1972).
- ⁸ Berger, J., Rachlin, A. I., Scott, W. E., Sternback, L. H., and Goldberg, J., *J. Amer. Chem. Soc.*, **73**, 5295 (1951).
- ⁹ Westley, J. W., Evans, R. H., Williams, T., and Stempel, A., *J. Chem. Soc. (Chem. Commun. D)*, **71** (1970).
- ¹⁰ Johnson, M. S., Merrin, J., Liu, S. J., and Paul, I. C., *J. Amer. Chem. Soc.*, **92**, 14 (1970).
- ¹¹ Pressman, B. C., *Symposium on mechanism of antibiotic action 56th Federation of American Societies for Experimental Biology Meeting*, Atlantic City (1972).
- ¹² Eletr, S., and Inesi, F., *Biochim. Biophys. Acta*, **282**, 174 (1972).
- ¹³ Martonosi, A., and Feretos, R., *J. Biol. Chem.*, **239**, 648 (1964).
- ¹⁴ Levy, J. V., in *Methods in Pharmacology* (edit. by Schwartz, A.), **1**, 77 (Appleton-Century-Crofts, NY, 1971).

Active Transport of L-Dopa in the Intestine

IN a discussion of the problems associated with the metabolism and absorption of L-3,4-dihydroxyphenylalanine (L-dopa) in patients with Parkinson's disease¹, Bianchini *et al.* suggested that the small intestine is the major site of absorption, as is the case with many other amino-acids. The existence of a carrier-mediated transport process was implied by the suggestion that the absorption of L-dopa is subject to competitive inhibition by other amino-acids. But a study² of the absorption of ¹⁴C-L-dopa *in vitro* by sacs of everted rat intestine did not suggest an active transport mechanism. On the contrary, there was no significant difference in mucosal uptake when the tissue was gassed with oxygen or rendered anoxic with nitrogen. These data appeared to be consistent with a passive diffusion mechanism for the entry of L-dopa into the mucosa of both stomach and small intestine. On the other hand, there is evidence that L-dopa inhibits the absorption of L-phenylalanine and L-tyrosine in patients with Parkinson's disease³. We have now investigated whether there is an active component in the L-dopa transport mechanism in the small intestine of the rat *in vitro*.

Male Sprague-Dawley rats (250–300 g) fed *ad lib.* were killed by a blow on the head. The small intestine between the common bile duct and the caecum was removed quickly, washed through with 20 ml. of normal saline and everted on a length of polythene tubing. Within 5 min of the death of the animal, the everted intestine was incubated at 37° C in Krebs-Ringer bicarbonate buffer in the oxygenated organ bath system of Wade and Bauckham (manuscript in preparation). The technique is a modification of that described by Fisher and Parsons⁴, but differs in that the whole of the small intestine is used and is everted before incubation. The mucosal fluid is continually oxygenated while a constant circulation of serosal fluid is maintained. The system also facilitates sampling from either side of the intestine at any time.

Initial serosal and mucosal volumes were 40 ml. and 60 ml. respectively, and the duration of each experiment was either 30 or 60 min. Tissues were oxygenated by gassing continuously with oxygen (95%) and carbon dioxide (5%) and rendered anoxic by replacing the gas mixture with nitrogen. All incubation media contained D-glucose (250 mg%).

L-Dopa was assayed by gas liquid chromatography. Aliquots of acidified incubation media (0.2 ml.) were evaporated to dryness on a rotary evaporator at 40° C. The trifluoroacetate derivative was prepared by dissolving the residual L-dopa in 0.2 ml. of tetrahydrofuran and adding

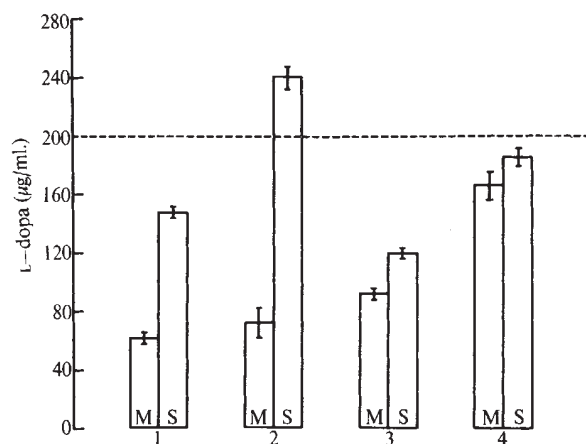


Fig. 1 The effects of anoxia and Ro4-4602 on the concentration gradients of L-dopa established after 60 min of incubation. At least four animals were in each group and the column heights indicate the mean values $\pm$ the standard error of the mean. M, Concentration in mucosal fluid; S, concentration in serosal fluid. Groups 1 and 2 gassed with 95% O₂, 5% CO₂; groups 3 and 4 gassed with nitrogen; groups 2 and 4 contained 200 µg/ml. Ro4-4602 in both mucosal and serosal media. The initial concentration of L-dopa in both mucosal and serosal media is shown by the dotted line.

0.03 ml. of trifluoroacetic anhydride. After at least 10 min at room temperature, 5 µl. aliquots of the reaction mixture were injected into a Bendix series 2500 gas chromatograph fitted with a flame ionization detector. Chromatography conditions were as follows. The column was of glass 6 feet long, with an inner diameter of 4 mm; it was packed with 6% QFI (trifluoropropyl methylsilicone polymer, Supelco Inc., Bellefonte, Pennsylvania) on Supelcoport 100/120 mesh. The temperature of the column was 155° C, of the inlet 165° C, and of the detector 165° C. Nitrogen carrier flowed at a rate of 50 ml./min, hydrogen at 40 ml./min and air at 200 ml./min. Relevant standards were included in each series of assays.

Beginning with 200 µg/ml. (10⁻³ M) L-dopa on both sides of the intestine, a concentration gradient was evident after 60 min of incubation (Fig. 1). The capacity of the small intestine to degrade L-dopa has previously been demonstrated in the rat². The extent of intestinal degradation of L-dopa in the present experiment was reflected by the fall in concentration of the drug on both sides of the intestine. The decrease in concentration on the serosal side was significantly inhibited by the addition of an L-dopa decarboxylase inhibitor (N-(DL-seryl-N'-2,3,4-trihydroxybenzyl)-hydrazine (Ro4-4602, 20 mg%, Hoffmann-La Roche) to the incubation media at the beginning of the experiment.

In the presence of the decarboxylase inhibitor, the concentration of L-dopa in the serosal fluid increased beyond the starting concentration while the mucosal uptake was not significantly influenced. Anoxia markedly reduced the gradient developed, indicating some dependence on oxidative metabolism (Fig. 1).

The separate and combined effects of anoxia and Ro4-4602 provide further insight into the mechanism of mucosal uptake of L-dopa. When the supply of oxygen was maintained, inhibition of the enzymatic decarboxylation of L-dopa had only a slight effect on mucosal uptake after 1 h. In the anoxic preparation, however, inhibition of L-dopa metabolism markedly inhibited mucosal uptake. This suggests that enzymatic decarboxylation has a regulating effect on the passive diffusion of the drug into the intestinal mucosa by its influence on the concentration gradient. On the other hand, "active" uptake seems to be the rate-limiting factor in the movement of drug into the oxygenated gut, with passive diffusion playing only a minor role.

When the experimental period was reduced from 1 h to 30 min and L-dopa was omitted from the serosal side, there was no inhibition of mucosal uptake in the presence of Ro4-4602 alone (Table 1), while the additive inhibitory effect of anoxia remained highly significant.

Table 1 Mucosal Uptake of L-Dopa *in vitro*

Isomer	Alteration to standard incubation conditions	No. of expts.	Conc. of L-Dopa in mucosal fluid at 30 min (mean $\pm$ s.e.) µg/ml.
L-Dopa	—	5	90 $\pm$ 6
	Ro4-4602	5	94 $\pm$ 5
	Anoxia	4	141 $\pm$ 7
	Anoxia + Ro4-4602	3	166 $\pm$ 6
	15 mM L-leucine	3	177 $\pm$ 6
	10 mM D,L-phenylalanine	2	126 $\pm$ 2
D-Dopa	—	4	171 $\pm$ 2

All incubations were carried out in Krebs-Ringer bicarbonate buffer, pH 7.4 at 37° C, containing glucose (250 mg%). Incubation media were gassed with oxygen (95%) and carbon dioxide (5%) or rendered anoxic with nitrogen. Leucine and phenylalanine were present in the mucosal fluid only. Ro4-4602 was present on both sides of the intestine. Initial concentration of L-dopa in all experiments was 10⁻³ M.

Other data (Table 1) show that the uptake of L-dopa has two further characteristics of an active transport process. Inhibition of uptake by other amino-acids was demonstrated by the marked decrease in the rate of disappearance of L-dopa from the mucosal fluid when in the presence of 15 mM L-leucine. The inhibition was significant but less marked in the presence of 10 mM D,L-phenylalanine. Second, comparison of the absorption rates of D-dopa and L-dopa showed that the latter was more readily absorbed. This was in accord with data⁵ which clearly demonstrated the stereospecificity of intestinal amino-acid transport, such that only the L-isomers of most of the naturally occurring amino-acids were absorbed by an "active", saturable mechanism.

Preliminary experiments in this laboratory on the kinetics of mucosal uptake of L-dopa indicate that the relationship between the reciprocals of initial rate of uptake and initial concentration is characteristic of a saturable process of the Michaelis-Menten type (Fig. 2). Extrapolation for the trans-

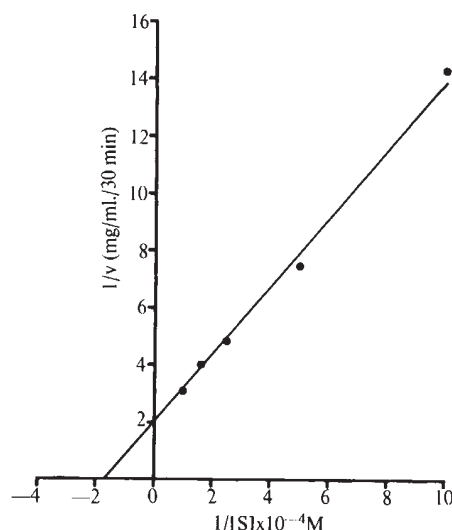


Fig. 2 The uptake of L-dopa by the everted small intestine of the rat shown as a Lineweaver-Burk plot. The half-saturation constant (K_t) is 5.9 mM.

port constant (K_t) gave a half-saturation concentration of 5.9 mM.

We interpret the data discussed here as evidence for the existence of an active transport mechanism for the intestinal absorption of L-dopa. The drug can be accumulated against a concentration gradient. Its absorption can be inhibited by anoxia and the presence of other amino-acids. The L-isomer is absorbed preferentially and its absorption appears to be saturable and characteristic of a carrier mediated or other saturable process.

The existence of a similar L-dopa absorptive mechanism in man may explain some of the problems associated with the absorption and the bioavailability of various dose forms. A relatively slow absorption rate from the stomach, where active transport of nutrients has not been demonstrated, would be predicted. Further, it would be expected that protein and perhaps other foodstuffs taken with an oral dose of L-dopa would inhibit the absorption of the drug from the intestinal lumen. Such an effect has been demonstrated on the absorption of tryptophan in man⁶. Being one of the few drugs absorbed by active transport, L-dopa would be subject to a greater variety of bioavailability effects than drugs which are absorbed by passive diffusion alone.

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- ¹ Bianchine, J. R., Calimlim, L. R., Morgan, J. R., Dujovne, C. A., and Lasagna, L., *Ann. NY Acad. Sci.*, **179**, 126 (1971).
- ² Rivera-Calimlim, L., Morgan, J. P., Dujovne, C. A., Bianchine, J. R., and Lasagna, L., *Biochem. Pharmacol.*, **20**, 3051 (1971).
- ³ Van Woert, M. H., *Clin. Pharmacol. Ther.*, **12**, 2, 368 (1971).
- ⁴ Fisher, R. B., and Parsons, D. S., *J. Physiol.*, **110**, 36 (1949).
- ⁵ Wiseman, G., in *Handbook of Physiology* (edit. by Code, C. F.), Section 6, 3, Ch. 67, 1277 (Amer. Physiol. Soc., Washington, DC, 1968).
- ⁶ French, G. P., and Wertz, A. W., *J. Nutr.*, **73**, 57 (1961).

Event Related Slow Potential Changes in Human Brain Stem

A SLOW negative shift of brain electrical potential can indicate association made between paired stimuli when one acts as a warning and the other an imperative stimulus¹. This is termed the contingent negative variation (CNV). Intracerebral recording in man confirmed the cortical origins of the change seen at the scalp. There have, however, been suggestions based on animal studies²⁻⁵ that, although essentially a cortical change, the CNV might be mediated by the action of sub-cortical centres, possibly in the thalamus and/or the brain stem and midbrain reticular system. Haider *et al.* recording from electrodes in thalamus and on the cortex of patients undergoing acute thalamic surgery, have reported characteristic changes in evoked potentials from the ventro-oral nucleus accompanying the appearance of the CNV at the cortex^{6,7}.

Recently the opportunity arose for us to study such responses in two patients with electrodes implanted in brainstem structures. Although electrode placement was not identical in both cases the overall distribution of electrodes was very similar. For convenience the results presented have been drawn from one patient, the general pattern of findings being almost identical in the two cases.

The patient was a 57 yr old woman who had suffered a cerebral thrombosis two years previously giving rise to a moderate left hemiparesis and the appearance of a thalamic syndrome. There was painful hyperaesthesia with sensory impairment over

the entire left half of the body and face. Thirty-four 150 μ m diameter gold electrodes had been implanted in the brain using stereotaxic procedures in preparation for treatment for the condition of intractable pain. The electrodes were in five sheaves which straddled the right thalamus. Each electrode was 4 mm long and separated from the next by 2 mm. Locations were estimated on the basis of X-ray photographs and the calculation of distances from known reference points⁸. On this basis the most rostral electrodes in each of the five sheaves were located within or adjacent to the caudate nucleus and the pes coronae radiatae, possibly with some extension into the lateral ventricle. The most caudal electrodes were in the lateral mesencephalic nucleus, peripeduncular nucleus, substantia nigra, pes pedunculi, medial and lateral lemniscus. The intermediate electrodes extended through the following thalamic nuclei: reticular, dorsooralis, zentrolateralis, ventrocaudalis, ventro-intermedius, ventrooralis and the medial geniculate body. There were also extensions into the internal capsule.

Twenty-seven electrodes were selected for study and each was referred to a common intrathalamic reference composed of the remaining seven electrodes. These seven, grouped towards the centre of three of the sheaves, were chosen because of a relatively low level of intrinsic and evoked activity during a preliminary series of tests. Simultaneous recording was carried out from a silver-silver chloride electrode at the scalp vertex referred to a linked pair of similar electrodes on the mastoid processes. A further pre-frontal electrode was used as a control for eye movements.

A 16-channel EEG was recorded through high gain amplifiers with input impedance of 100 Mohm and using time constants ranging from 1.2 to 5 s. On-line averaging was carried out using a PDP 12 computer. Additional averaging and analysis was undertaken off-line. Five test sessions took place from one to two weeks after implantation of the electrodes. No electrocoagulative treatment had been carried out at that stage but the patient was alert and cooperative.

In the slow potential test session paired presentations of click (S_1) followed by repetitive flashes (S_2) were used. Initially the patient was required to make no motor response. Later she was asked to press a button as quickly as possible with her right hand to terminate S_2 . The S_1 - S_2 interstimulus interval was 1 s and a total of 128 irregularly spaced trials were carried out. Trials were averaged online in sets of eight.

Widespread slow potential changes were observed from brainstem electrodes during the S_1 - S_2 + response condition, those from the most rostral electrodes being positive with respect to the intrathalamic reference and those from the most caudal (mesencephalic) electrodes negative. The intermediate electrodes in each sheaf, those in thalamic nuclei, showed little or no slow shifts (Fig. 1). The form and duration of the slow changes from the caudal electrodes closely resembled the vertex CNV and the positive shift seen at the rostral electrodes constituted a phase reversal of the caudal response components. Amplitudes and onset latencies of the slow potential shifts observed are given in Table 1. Because of the short intrinsic time constant of gold electrodes, the amplitudes of slow shifts measured sub-cortically were probably about 20% less than the true values.

Choice of an intrathalamic reference made interpretation of the phase inversion between rostral and caudal electrodes equivocal. Six sub-cortical electrodes showing clear evidence

Table 1 Amplitude and Latency Onset of Slow Potential Shifts

Electrode location	Slow potential change	
	Amplitude (mean level for 200 ms preceding S_2)	Latency to onset
Scalp (Cz)	-9 μ V	470 ms
Sub-cortical (rostral to thalamus)	+4 μ V to +10 μ V	340 to 360 ms
Thalamus	+2 μ V to -3 μ V	—
Mesencephalon	-5 μ V to -25 μ V	230 to 280 ms

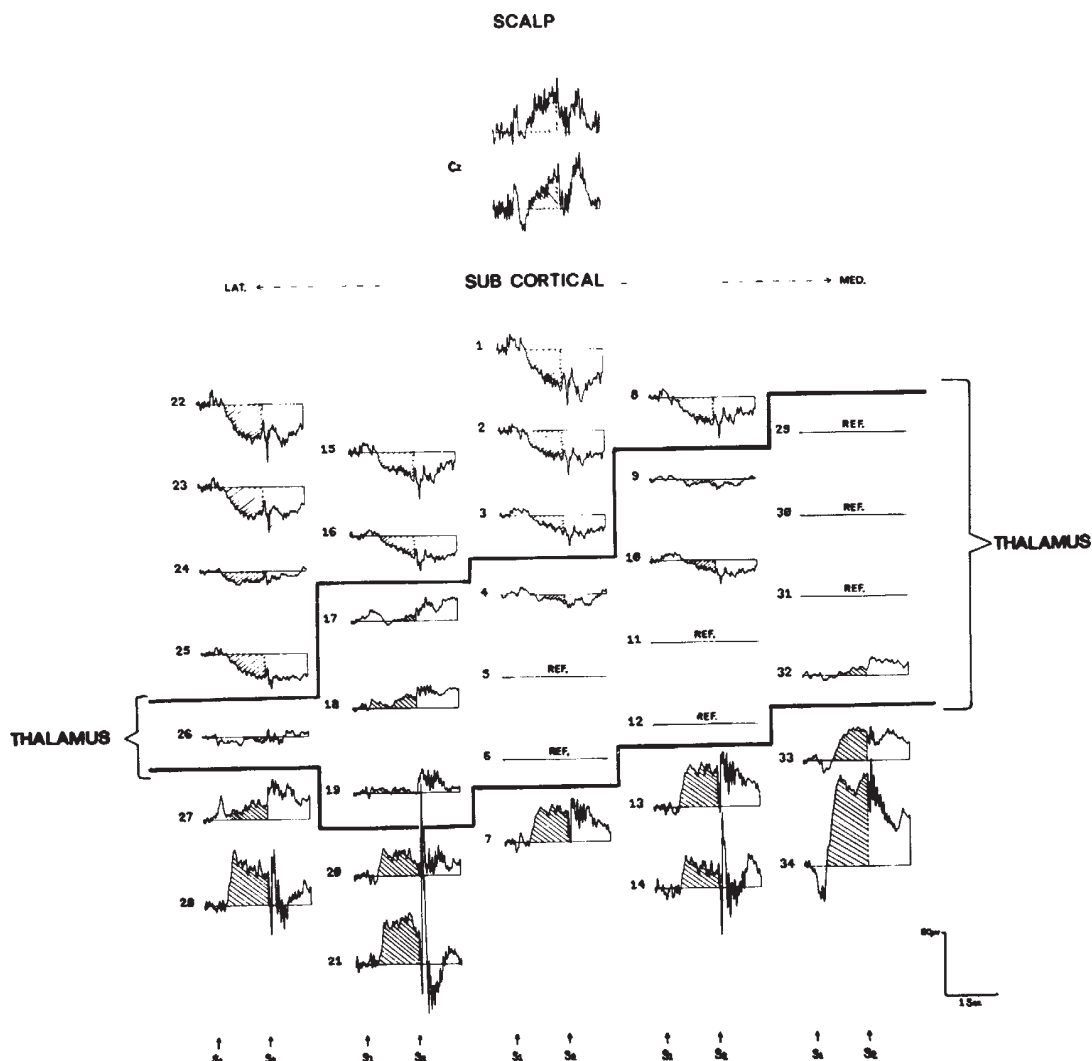


Fig. 1 Diagrammatic layout of averaged CNVs ($N=40$) recorded from the scalp and brainstem. Electrode C_2 is referred to linked mastoids. Each sub-cortical electrode has a common reference composed of electrodes 5, 6, 11, 12, 29, 30, 31, selected for their low level of evoked activity. S_1 is a click, S_2 are repetitive flashes terminated by a button press. Calibration is $20 \mu V$. There is a prominent CNV at the most caudal (midbrain) electrodes and a corresponding positive variation at the most rostral extra-thalamic electrodes.

of slow potential changes were therefore selected to conduct a comparison of the scalp and intra-thalamic references. Each electrode was referred both to the intra-thalamic reference and, on a separate channel, to the mastoid reference. The waveform and polarity of slow potential change at a given electrode was found to remain the same irrespective of whether the reference was thalamic or mastoid.

Evoked potentials to single click, flash and somato-sensory stimuli were also recorded. They showed distributions very similar to that of the CNV; the largest responses were observed from mesencephalic structures, smaller responses were seen from more rostral extra-thalamic and caudate nucleus electrodes and, in the case of flashes and clicks, there were indications of small, but consistent responses from some electrodes within the thalamus itself. The most prominent component to flash and click stimuli was a negative peak with a latency of 92 ms (or slightly later at some locations). An earlier but less prominent negative peak was seen between 42 and 48 ms after flash stimuli and at 62 ms after click stimuli. The somato-sensory stimulus, consisting of electrical stimulation of the right (ipsilateral) median nerve at the right wrist, elicited responses, principally in mesencephalic structures.

The extent to which habituation of evoked potentials could be observed in the brainstem was investigated by selecting four

electrodes, which had shown clear responses to an irregular flash, and observing their responses to similar flashes presented at regular intervals. 160 flashes were presented at intervals of 1.5 s and 80 at intervals of 1.0 s. Trials were averaged in sets of four to observe any trend towards habituation. Electrodes 14, 20 and 21, located in midbrain, showed little evidence of habituation at either interval. At electrode 1, the most rostral of the group, the principal response component observed during irregular flash stimulation had been a negative peak with a latency of 112 ms. During regular stimulus presentation at intervals of 1.5 s this component was absent on at least half of the averages. During regular presentation at the 1.0 s interval it was no longer observable.

The findings, from both patients, of CNVs in mesencephalic structures and the presence of simultaneous positive variations in more rostral extrathalamic white matter and caudate nucleus are generally consistent with those of Rebert⁴ in Macaque monkeys performing a discriminative foreperiod reaction-time task. The evidence clearly implicates the diffuse and so-called non-specific projection systems of the brain in man in a situation involving the association of incoming signals. It demonstrates some aspects of the temporal relationships between subcortical and cortical processing and indicates that both long latency evoked potentials and slow potentials are

processed by essentially the same brainstem structures. Nevertheless the diversity of patterns encountered and the results of habituation suggest that these diffusely acting systems are capable of more than an undifferentiated arousal response.

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- ¹ Walter, W. G., Cooper, R., Aldridge, V. J., McCallum, W. C., and Winter, A. L., *Nature*, **203** 380 (1964).
- ² Rebert, C. S., and Irwin, D. A., *Electroenceph. Clin. Neurophysiol.*, **27**, 152 (1969).
- ³ Borda, R. P., *Electroenceph. Clin. Neurophysiol.*, **29**, 173 (1970).
- ⁴ Rebert, C. S., in *Event Related Slow Potentials of the Brain: Their Relation to Behavior* (edit. by McCallum, W. C., and Knott, J. R.) (in the press).
- ⁵ McSherry, J. J., in *Event Related Slow Potentials of the Brain: Their Relation to Behavior* (edit. by McCallum, W. C., and Knott, J. R.) (in the press).
- ⁶ Haider, M., Ganglberger, J. A., and Groll-Knapp, E., *Acta Neurol. Latinoamer.*, **14**, 132 (1968).
- ⁷ Haider, M., in *Attention: Contemporary Theory and Analysis* (edit. by Mostofsky, D. I.), 419 (Appleton-Century-Crofts, New York, 1970).
- ⁸ Schaltenbrand, G., and Bailey, P., *Introduction to Stereotaxis with an Atlas of the Human Brain* (Grune and Stratton, 1959).

Hapten-reactive Helper Lymphocytes

SINCE the discovery of the synergism between lymphocytes derived from the thymus (T cells) and those originating in the bursa or bone marrow (B cells) in the induction of humoral antibody synthesis¹⁻³, numerous studies have been carried out to establish, (1) if both T and B cells show specific immunocompetence, and (2) how they express their potential competence.

Both T and B cells have a specific immunological memory¹⁻⁵, and so have been assumed to bear specific receptors for antigen. The receptors on B lymphocytes are immunoglobulins⁶⁻⁸ and their specificity seems to be very similar to that of serum

antibodies^{6,9}. T cells also have antigen-binding receptors¹⁰⁻¹², but direct study of the nature of T cell receptors has met with difficulties⁹. Several attempts have therefore been made to characterize indirectly the receptor(s) according to the selective effect of various immunogens on the function of normal or primed T lymphocytes¹³⁻¹⁵. Contradictory results have been obtained¹³⁻¹⁵ from studies to establish whether T and B cells carry receptors which recognize the same spectrum of antigenic specificities.

Hapten-specific B cells have been demonstrated unequivocally^{6,9,16}, so evidence for the existence of hapten-specific T cells will be important. Hapten-reactive T lymphocytes have been found in functional tests¹⁷⁻²⁰ and in hapten-binding assays¹⁶. An example of the former is the helper function of DNP-reactive (dinitrophenyl) lymphocytes from animals whose skins were painted with DNP. Cells from mice immunized with bovine serum albumin (BSA) were depleted of T cells and admixed with the DNP-reactive lymphocytes. On stimulation with DNP-BSA, an augmented anti-BSA response was obtained. The functional criteria for the helper effect being due to T cells was the demonstration that the skin-painted mice elicited strong delayed hypersensitivity to DNP¹⁹. Direct proof for the helper effect being ascribed to T lymphocytes is, however, still missing. The helper effect could be due to (1) T lymphocytes¹⁷⁻²⁰, (2) anti-DNP antibodies²¹, or (3) anti-DNP antibody coated or "armed" macrophages²².

To distinguish between these, cells from mice whose skins had been painted with DNP were treated as follows. (1) They were purified on anti-immunoglobulin coated columns (anti-IgM columns) which selectively retain B lymphocytes⁸. (2) They were then treated with anti- θ antiserum plus complement, which according to Raff²³ should eliminate T lymphocytes.

The advantage of using these two techniques in parallel is that the column separation also eliminates cells with cytophilic, surface, adherent anti-DNP antibodies, whereas the anti- θ treatment might not. The experimental design used was similar to that described by Mitchison¹⁸. Mice were immunized with 200 μ g BSA in Freund's complete adjuvant (CFA), and BSA immune spleen and lymph node cells were collected from these animals 1-3 months later. Some of the cells were treated *in vitro* with anti- θ antiserum plus complement⁹ to eliminate BSA-specific T cells, which will be called B anti-BSA cells. Other mice had their skin painted with dinitrofluorobenzene (DNPF) 6-7 days before transfer or were immunized with DNP₆MSA (mouse serum albumin) or DNP₇OA (ovalbumin) 3-6 weeks before transfer. Cells from these animals were used either untreated, after passage through an anti-IgM column or after anti- θ plus complement treatment. These will be called helper cells. B anti-BSA and helper anti-DNP

Table 1 DNP-reactive Helper Lymphocytes

Group No.	B cells *	Anti- θ †	Helper cells ‡	Column§	Antigen	Anti-BSA antibodies¶	
						Log ₂ titre	Log ₁₀ ABC
1	10 ⁷ BSA	—	—	—	DNP ₆ BSA	11.7 ± 1.25	2.84 ± 0.13
2	10 ⁷ BSA	+	2 × 10 ⁷ NC	—	DNP ₆ BSA	4.8 ± 0.94	0.76 ± 0.23
3	10 ⁷ BSA	+	2 × 10 ⁷ DNP-Skp	—	DNP ₆ BSA	7.1 ± 0.54	1.19 ± 0.15
4	10 ⁷ BSA	+	2 × 10 ⁷ DNP-Skp	+	DNP ₆ BSA	8.2 ± 1.02	1.77 ± 0.18
5	10 ⁷ BSA	+	2 × 10 ⁷ DNP ₆ MSA	—	DNP ₆ BSA	7.1 ± 0.67	1.54 ± 0.14
6	10 ⁷ BSA	+	2 × 10 ⁷ DNP ₆ MSA	+	DNP ₆ BSA	7.9 ± 1.02	2.10 ± 0.22
7	10 ⁷ BSA	—	—	—	—	3.2 ± 0.71	0.69 ± 0.17
8	—	—	2 × 10 ⁷ DNP-Skp	—	DNP ₆ BSA	0.2 ± 0.49	Neg.

* B cells, mixed spleen and lymph node cells from CBA × Balb/c mice immunized 8 weeks before transfer.

† —, BSA immune cells treated with complement only (guinea-pig serum diluted 1:4 in BSS); +, BSA immune cells treated with anti- θ antiserum plus complement⁹.

‡ Helper cells: NC = normal lymph node cells; DNP-Skp = cells from mice painted with 500 μ g DNPF 7 days before transfer. DNP₆MSA = mixed spleen and lymph node cells from DNP₆MSA immune mice (3 week immune).

§ —, Non-passed cells; +, cells passed through an anti-IgM coated column. (% θ positive cells: DNP-Skp-C = 65; DNP₆MSA-C = 49; DNP-Skp-P = 93; DNP₆MSA-P = 89.)

|| Antigen (10 μ g) given together with the cells.

¶ Log₂ titre, log₂ haemagglutination titre against DNP₇OA-SRBC (2-ME resistant titre ± one s.d.); ABC, antigen binding capacity at 0.001 μ g BSA: ¹²⁵I/ml. ± one s.e.

Table 2 DNP-reactive Helper T Lymphocytes

Group No.	B cells *	Helper cells †	Column ‡	Anti-θ §	Antigen	Anti-BSA antibodies ¶	
						Log ₂ titre	Log ₁₀ ABC
1	5 × 10 ⁶ BSA	2 × 10 ⁷ NC	—	—	DNP ₅ BSA	5.2 ± 0.51	0.20 ± 0.14
2	5 × 10 ⁶ BSA	3 × 10 ⁷ DNP-Skp	—	—	DNP ₅ BSA	8.9 ± 1.02	1.48 ± 0.09
3	5 × 10 ⁶ BSA	1 × 10 ⁷ DNP-Skp	—	—	DNP ₅ BSA	7.2 ± 0.51	0.75 ± 0.07
4	5 × 10 ⁶ BSA	3 × 10 ⁷ DNP-Skp	+	—	DNP ₅ BSA	10.4 ± 1.33	1.76 ± 0.13
5	5 × 10 ⁶ BSA	1 × 10 ⁷ DNP-Skp	+	—	DNP ₅ BSA	9.1 ± 1.26	1.41 ± 0.13
6	5 × 10 ⁶ BSA	3 × 10 ⁷ DNP-Skp	—	+	DNP ₅ BSA	4.5 ± 0.89	0.16 ± 0.25
7	5 × 10 ⁶ BSA	1 × 10 ⁷ DNP-Skp	—	+	DNP ₅ BSA	4.7 ± 0.81	0.38 ± 0.24
8	5 × 10 ⁶ BSA	2 × 10 ⁷ NC	—	—	Sulph ₅ BSA	5.2 ± 0.68	0.24 ± 0.19
9	5 × 10 ⁶ BSA	2 × 10 ⁷ DNP-Skp	—	—	Sulph ₅ BSA	5.1 ± 1.02	0.57 ± 0.22
10	5 × 10 ⁶ BSA	—	—	—	—	5.0 ± 1.14	0.44 ± 0.29
11	5 × 10 ⁶ NC	2 × 10 ⁷ DNP-Skp	—	—	DNP ₅ BSA	0.8 ± 0.51	Neg.

* Spleen cells from CBA × Balb/c mice immunized 12 weeks before transfer. They were treated with anti-θ antiserum plus complement⁹.

† NC, Normal lymph node cells; DNP-Skp = see Table 1.

‡ —, Non-passed cells; +, cells passed through an anti-IgM coated column. (% θ positive cells: DNP-Skp-C = 69%, anti-MIg passed = 97%).

§ —, Non-treated; +, anti-θ treated (number of anti-θ treated cells was adjusted so that the given numbers of live cells were transferred).

|| Antigen (10 µg) given together with the cells.

¶ See Table 1.

cell populations were mixed *in vitro* and injected together with DNP₅BSA (or with Sulph₅BSA = sulphonylated BSA as specific control) into sublethally irradiated syngeneic recipient mice (500 R). The mice were bled 10 days later. Individual antisera were tested for anti-BSA antibodies by haemagglutination⁹ and by a modified Farr assay²⁴.

A representative experiment showing the impact of anti-MIg columns on the helper effect of lymph node cells from (DNP-Skp) mice whose skins had been painted with DNP and from DNP-MSA immune mice can be seen in Table 1. Both control and anti-IgM column passed DNP-reactive lymphocytes were very active as "helpers", the latter cells being the most active⁸. The same result was obtained in three more similar experiments. In one of these DNP-OA immune cells were used instead of DNP-MSA immune cells. Again, either control or anti-IgM column passed cells functioned as "helpers". The anti-IgM column passed cells were tested for DNP-specific rosette-forming cells⁹ (RFC) before and after passage. The figures for the experiment in Table 1 were: before passage; DNP-Skp = 2,750 ± 298 RFC/10⁶ lymphoid cells (± one s.d.), DNP-MSA cells = 7,890 ± 305 RFC/10⁶ cells: after passage; DNP-Skp = 90 ± 85 RFC/10⁶ cells and DNP-MSA cells = 105 ± 75 RFC/10⁶ cells. In summary these results indicate (1) that the helper cell belongs to the class of lymphocytes having very little if any conventional immunoglobulin on their surface (T cells) and (2) that removal of B cells and free or cell-bound anti-DNP antibodies had no impact on the helper function observed.

Table 2 shows an experiment where (1) the effect of anti-IgM column passage, (2) the effect of anti-θ antiserum plus complement and (3) the specificity of cells from mice painted with DNP was tested using two different doses of helper cells. As in Table 1, anti-IgM column passage increased the helper capacity of DNP-reactive lymphocytes; treatment with anti-θ antiserum plus complement abolished the helper capacity; and the helper effect observed was specific. Two more experiments proved the abolishing effect of anti-θ antiserum plus complement on DNP-reactive helper cells. In summary, these experiments demonstrate the existence of the hapten-specific helper effect of T lymphocytes.

Other studies in this laboratory have failed to demonstrate a helper effect of anti-hapten antibodies²¹ or antibodies directed against the new antigenic determinants introduced in MSA by the haptenic coupling (Rubin, unpublished). Help by antibodies was, however, found in a similar system in the rabbit²⁵. The failure of others²¹ to demonstrate DNP-specific helper cells might be due to (1) the dose of DNPF applied (500 µg DNPF seemed to be optimal in our system), (2) the time between immunization and collection of immune cells²⁶,

and (3) the number of cells used. Five out of six experiments have shown that in order to get a significant helper effect, 2 × 10⁷ DNP-reactive cells or more were needed (exception, Table 2). Cell dilution studies with BSA-immune and DNP-reactive cells, unpassed or anti-IgM column passed cells, have shown that whereas 2 × 10⁷ DNP reactive cells are needed for a significant helper function, only 10⁶ BSA immune (anti-IgM passed) or 5 × 10⁶ unpassed BSA immune cells are needed for a significant BSA helper function (Rubin and Wigzell, unpublished).

Whether the DNP-reactive T lymphocytes demonstrated in this paper show the same specificity as humoral anti-DNP antibodies and anti-DNP B lymphocytes is still unknown. Studies using DNP-BSA conjugates with DNP coupled to BSA by different procedures to induce different new antigenic determinants in the BSA molecule (Rubin and Aasted, unpublished results) might solve this problem.

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- Claman, H. N., Chaperon, E. A., and Triplett, R. F., *Proc. Soc. Exp. Biol. Med.*, **112**, 1167 (1966).
- Mitchell, G. F., and Miller, J. F. A. P., *J. Exp. Med.*, **128**, 821 (1968).
- Taylor, R. B., *Transplant. Rev.*, **1**, 114 (1969).
- Mond, J. J., Takahashi, T., and Thorbecke, G. J., *J. Exp. Med.*, **136**, 663 (1972).
- Miller, J. F. A. P., Sprent, J., Basten, A., Warner, N. L., Breitner, J. C. A., Rowland, G., Hamilton, J., Silver, H., and Martin, W. J., *J. Exp. Med.*, **134**, 1266 (1971).
- Wigzell, H., and Mäkelä, O., *J. Exp. Med.*, **132**, 110 (1970).
- Walter, C. S., and Wigzell, H., *J. Exp. Med.*, **132**, 1233 (1970).
- Wigzell, H., Sundquist, K. G., and Yoshida, T. O., *Scand. J. Immunol.*, **1**, 75 (1971).
- Rubin, B., and Wigzell, H., *J. Exp. Med.*, **137** (in the press).
- Basten, A., Miller, J. F. A. P., Warner, N. L., and Pye, J., *Nature New Biology*, **231**, 104 (1971).
- Roelants, G. E., and Askonas, B. A., *Eur. J. Immunol.*, **1**, 151 (1971).
- Hogg, N. M., and Greaves, M. F., *Immunology*, **22**, 967 (1972).
- Rajewsky, K., and Pohlitz, H., *Progr. Immunol.*, **1**, 357 (1971).
- Senyk, G., Williams, E. B., Nitecki, D. E., and Goodman, J. W., *J. Exp. Med.*, **133**, 1294 (1971).
- Schirmacher, V., and Wigzell, H., *J. Exp. Med.*, **136**, 1616 (1972).
- Möller, E., Bullock, W., and Mäkelä, O., *Eur. J. Immunol.* (in the press).

- ¹⁷ Iverson, G. M., *Nature*, **227**, 273 (1970).
- ¹⁸ Mitchison, N. A., *Eur. J. Immunol.*, **1**, 65 (1971).
- ¹⁹ Taylor, R. B., and Iverson, G. M., *Proc. Roy. Soc., B*, **176**, 393 (1971).
- ²⁰ Iverson, G. M., in *Cell Interactions* (edit. by Silvestri, L. G.), **3** (North Holland Publ. Co., Amsterdam, 1971).
- ²¹ Janeway, C. R., and Paul, W. E., *Eur. J. Immunol.* (in the press).
- ²² Asherson, G. L., and Zembala, M., *J. Exp. Med.*, **132**, 1 (1970).
- ²³ Raff, M. C., *Transplant. Rev.*, **6**, 52 (1971).
- ²⁴ Celada, F., Schmidt, D., and Strom, R., *Immunology*, **17**, 189 (1969).
- ²⁵ Rubin, B., *Scand. J. Immunol.*, **1**, 125 (1972).
- ²⁶ Asherson, G. L., and Allwood, G. G., *Immunology*, **22**, 493 (1972).

- ¹ Burnet, F. M., *The Clonal Selection Theory of Acquired Immunity* (Cambridge University Press, Cambridge, 1959).
- ² Wilson, D. B., and Billingham, R. E., *Adv. Immunol.*, **7**, 189 (1967).
- ³ *Immunological Tolerance* (edit. by Landy, M., and Braun, W.) (Academic Press, New York, 1969).
- ⁴ Wegmann, T. G., Hellström, I., and Hellström, K. E., *Proc. US Nat. Acad. Sci.*, **68**, 1644 (1971).
- ⁵ Phillips, S. M., Martin, W. J., Shaw, A. R., and Wegmann, T. G., *Nature*, **234**, 146 (1971).
- ⁶ Wekerle, H., Cohen, I. R., and Feldman, M., *Nature New Biology*, **241**, 25 (1973).
- ⁷ Deol, M. S., and Whitten, W. K., *Nature New Biology*, **238**, 159 (1972).
- ⁸ Deol, M. S., and Whitten, W. K., *Nature New Biology*, **240**, 277 (1972).

Chimaeras and the Forbidden-clone Theory of Self-tolerance

THE forbidden-clone theory of self-tolerance, which postulates that if immunologically competent cells capable of anti-self reaction arise they are soon eliminated, was widely accepted for a long time¹⁻³, but it has recently been challenged⁴⁻⁶. Part of the challenge rests on the demonstration that a factor capable of blocking anti-self reaction is present in the serum, and part on *in vitro* studies indicating that cells capable of anti-self reaction occur in mice and rats. The studies with mice used chimaeras, also known as allophenic or tetraparental mice, which are made by fusing morulae of different genotypes. It is probably too early to say whether the forbidden-clone theory has been dethroned, but it may be pointed out that the studies with chimaeras are open to objection. As chimaeras may again be used for work of this nature, this objection is perhaps worth stating.

It is based on the fact that the two types of cells in a chimaera are not uniformly mixed throughout, and the mixture is generally far from intimate. Our examination of 10 chimaeras made from pigmented and unpigmented genotypes, all showing a good mixture of the two types of pigment cells in the fur, revealed that not only were large parts of the pigmentary layer of the retina of one kind or the other, but one retina was wholly pigmented, one almost wholly pigmented, and three almost wholly unpigmented⁷. The distribution of the migratory pigment cells in the iris, choroid and inner ear was similarly uneven⁸. To obtain a clearer picture, I examined the Harderian gland in the same animals. This is a large, thick structure, which almost surrounds the medial half of the eye, and is extremely rich in melanocytes. Two glands (in different animals) had no pigmented cells at all, and three had large parts that were entirely unpigmented. For obvious reasons it is impossible to say whether any gland was colonized solely by pigmented cells, but it is reasonable to assume that a comparable number might have been, the histological appearance of some being consistent with this assumption. Taking the entire cranial region, two chimaeras were unilaterally lacking in pigmented melanocytes of the migratory type, and one or two presumably in unpigmented ones.

If the chimaeras can be so wanting in uniformity in regard to pigment cells of both types, they may well have large regions in the thymus that are of single origin. An appreciable proportion of lymphocytes would then be expected to acquire their specificity in a region of their own genotype, and so be capable of reacting against cells of the other type. As the formation of lymphocytes is believed to be a continuous process, such cells would be found in the lymph nodes of chimaeras at all times, and their presence would not by itself rule out the mechanism implicit in the forbidden-clone theory as an additional factor in self-tolerance.

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Dislocations in Tobacco Mosaic Virus

I do not allege that the way Butler and Klug use "dislocation" is incorrect. I merely point out that as crystal dislocations occur in tobacco mosaic virus (TMV) and may perform important functions, "confusion is bound to arise if the term dislocation continues to be used loosely". Confusion is even more likely when the term is used in the same context by the same group in both strict ("screw dislocation"¹) and loose (for example on p. 133 of ref. 2, "step dislocation at the end of the single helical rod") senses.

Butler and Klug deny my statement that members of their group refer to helical forms being dislocated or containing a dislocation. The second quotation above is sufficient to show their denial is false. I can supply a corroboratory quotation from every source I cite.

There is nothing wrong with taking the disk as the reference—I find a different reference more convenient. My reference is similar to Klug's radial projection³, which he and his coworkers use elsewhere but not here.

Just as Butler and Klug found it necessary or convenient to present detailed models "to give some general feel for the process", so have I. Without detailed models an explanation would be difficult if not impossible. What may appear to them "differences in detail" are in fact important differences: as I explain, one of their mechanisms converts the disk directly to a portion of a helix with the same number of subunits per turn as in the completed virion whereas the other requires an additional step.

My mechanisms, based on theirs, depend no more on "continuity of the disk" than do theirs. Just because subunits can be gained or lost in no way rules out dislocations. On the contrary, a very important mode of movement of dislocations requires the loss or gain of subunits⁴. It is similar to the mechanism of climb that I describe.

In their final paragraph Butler and Klug express an opinion which I am confident will be proved wrong. What can be stated with certainty is that dislocations are present in many types of biological structures. The bibliography on dislocations in biological structures which I am compiling already contains more than a hundred references.

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- ¹ Butler, P. J. G., *Nature*, **233**, 25 (1971).
- ² Durham, A. C. H., thesis, University of Cambridge (1970).
- ³ Klug, A., Crick, F. H. C., and Wyckoff, H. W., *Acta Cryst.*, **11**, 199 (1958).
- ⁴ Harris, W. F., and Scriven, L. E., *Nature*, **228**, 827 (1970).

SV40 Protection in Myeloma Oncogenesis

SIMIAN virus SV40, a DNA tumour virus, causes a productive infection in both monkey and human cells, leading to lysis of the cells and release of infectious virus. In murine systems, however, the virus transforms the cells, leading to new virus-specific antigens on the transformed cells¹. These transformed cells induce tumours in mice which then respond to the tumour specific antigen^{2,3}. I report here protection of mice by SV40 when given with syngeneic myeloma tumour cells.

The myeloma line X5563, syngeneic for C₃H mice, was obtained from Dr M. Potter of the National Institutes of Health and has been maintained here *in vitro*. SV40 (obtained from Dr P. Naha of Mill Hill) was grown on BSC-1 cells, and titred 10^8 plaque-forming units (PFU) ml.⁻¹. The virus was inactivated 1 h in some studies, using a Hanovia germicidal lamp 14 cm away. Significance was tested using the Newman Keuls method of multiple comparison.

In the first experiment, groups of 50 C₃H female mice were inoculated i.p. with 1.5×10^6 viable cells in: (1) 0.2 ml. of tissue culture medium; (2) 0.2 ml. of active SV40; or (3) 0.2 ml. of ultraviolet-inactivated SV40. A fourth group received 0.2 ml. SV40 as an additional control. As seen in Fig. 1, deaths in the control group were first observed on day 48, and by day 57, 67% of the mice were dead. By contrast, in the group given myeloma and active SV40, deaths were first seen on day 55. Similarly, in the group given myeloma and inactivated virus, deaths were first observed on day 59. In both virus-treated groups, the mortality was significantly lower ($P < 0.05$) than the controls. Mice inoculated with SV40 had no evidence of tumour when killed 73 days after inoculation.

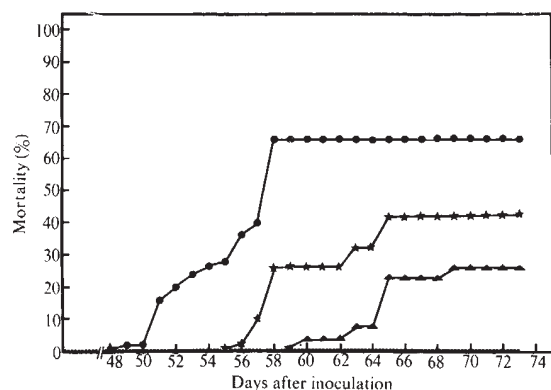


Fig. 1 Mice were inoculated i.p. with 7×10^5 myeloma cells (●), 7×10^5 myeloma cells in 0.2 ml. active SV40 (★), 7×10^5 myeloma cells in 0.2 ml. of inactive SV40 (▲), or 0.4 ml. of SV40 (---) on day 0. The animals were observed daily and deaths recorded.

To exclude the possibility that protection was conferred by factors from the BSC-1 (monkey) cells, on which SV40 was grown, mice were inoculated with 1.5×10^6 viable X5563 cells in 0.2 ml. BSC-1 conditioned medium. Myeloma cells were also inoculated with NIP-T4 phage (courtesy of Dr A. Cross) to determine if the presence of another viral antigen could confer the same protection seen with SV40. Neither groups was significantly protected against the myeloma cells. To exclude the possibility that SV40 lysed the cells, thus effectively lowering the number of cells given to the animal, 2×10^7 PFU SV40 was added to 1.5×10^6 cells in 0.2 ml. After 2 h the cells were washed and grown *in vitro*. There was no evidence of lysis.

Protection has been demonstrated in the above experiment when virus was given simultaneously with the tumour cell. In the following experiments, virus was given either before or after myeloma challenge to ascertain whether protection was achieved. Groups of 25 C₃H mice were inoculated with 1.5×10^6

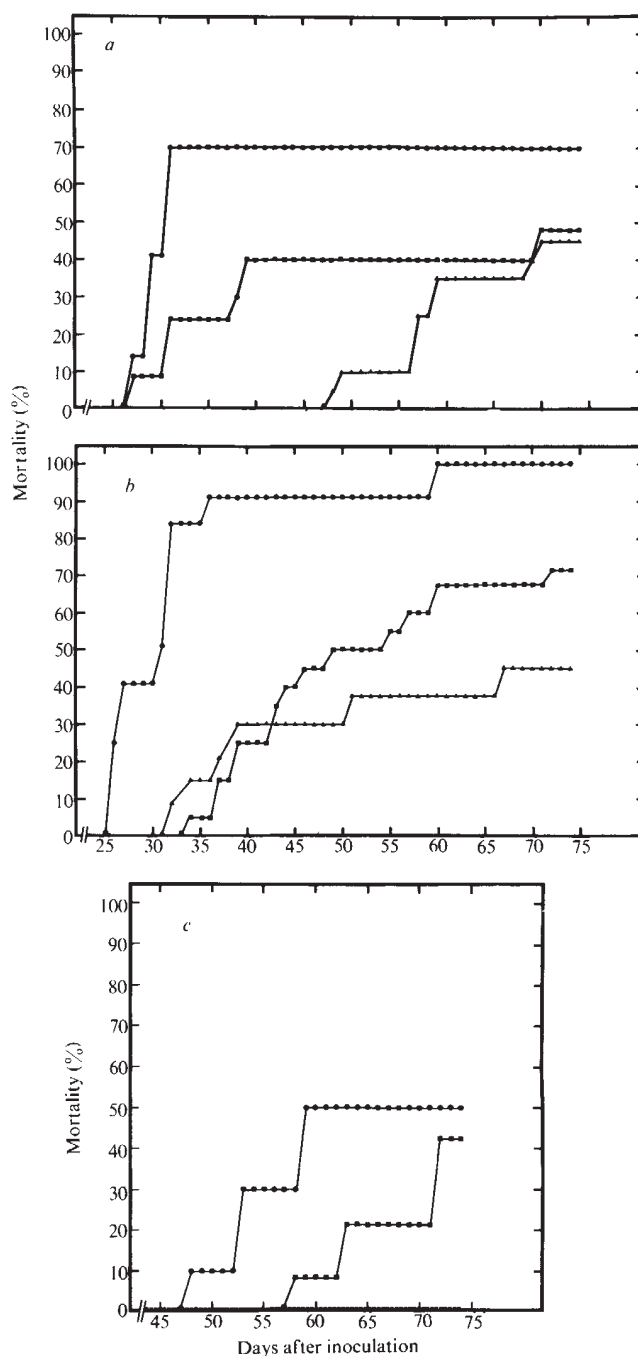


Fig. 2 a, Mice were inoculated i.p. with 1.5×10^6 myeloma cells on day 0 (●), 1.5×10^6 myeloma cells on day 0, 0.4 ml. of SV40 on day 2 (■), or 1.5×10^6 myeloma cells on day 0, 0.4 ml. of SV40 on day 13 (▲). b, Mice were inoculated i.p. with 1.5×10^6 myeloma cells on day 2 (●), 0.4 ml. of inactivated SV40 on day 0, 1.5×10^6 myeloma cells on day 2 (■), or 0.4 ml. of active SV40 on day 0, 1.5×10^6 myeloma cells on day 2 (▲). c, Mice were inoculated i.p. with 1.5×10^6 myeloma cells on day 13 (●), 0.4 ml. of active SV40 on day 0, 1.5×10^6 myeloma cells on day 13 (■), or 0.4 ml. of inactivated SV40 on day 0, 1.5×10^6 myeloma cells on day 13 (▲). In all cases animals were observed daily and deaths recorded.

viable tumour cells. One group received virus 2 days later, and the second group 13 days later. As seen in Fig. 2a, the groups treated with virus were significantly protected ($P < 0.001$). In the second experiment (Fig. 2b), groups of mice were pretreated with either active or inactive virus, and two days later, challenged with 1.5×10^6 tumour cells. Again, protection in the latter groups was significant ($P < 0.001$). In the final experiment (Fig. 2c), mice were pretreated with active or inactive SV40,

and inoculated with tumour cells 13 days later. Although preinoculating mice with active virus delayed the onset of death, the most significant protection was achieved when mice were pretreated with inactive virus. In this group, no animals died up to 75 days after inoculation.

These results show that SV40 protects mice against a tumour challenge of syngeneic myeloma cells. The protection occurring when the virus was given simultaneously with the tumour could be explained by adsorption of virus to the tumour cell surface, thus altering the antigenicity of the cell. It is more difficult to explain how the virus can protect when given up to 13 days before or after myeloma challenge; perhaps SV40 "homes in" on the cells *in vivo*. There is no evidence, based on the *in vitro* observations, that the cells are lysed. Why ultraviolet-inactivated virus should be more effective than live virus in protecting the host is still unclear. It is possible, based on work demonstrating *in vitro* repair of ultraviolet-damaged SV40 (ref. 4), that repair might have occurred *in vivo*, the virus thus becoming a source of new and varied antigen. Further studies are underway to elucidate the mechanism of SV40 protection.

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¹ Black, P. H., and Rowe, W. P., *Proc. Soc. Exp. Biol. Med.*, **114**, 721 (1963).

² Smith, R. W., Morganroth, J., and Mora, P. T., *Nature*, **227**, 141 (1970).

³ Tevethia, S. S., and Zarleng, J. M., *J. Retic. Soc.*, **11**, (4), 405 (1972).

⁴ Aaronson, S. A., *J. Virol.*, **6**, 393 (1970).

Depression of Immune Response to Moloney Leukaemia Virus by Malarial Infection

MALARIAL infection depresses the immune response to a variety of antigens in mice¹⁻⁶ and man^{7,8}. It has been postulated that malarial immunodepression is implicated in the development of a human neoplasm, Burkitt's lymphoma⁹, the geographical distribution of which coincides with that of holoendemic malaria¹⁰. In Swiss mice, malarial infection has been shown to increase the rate of spontaneous lymphomagenesis¹¹; and in adult Balb/c mice to potentiate the induction of lymphomas by the Moloney leukaemia virus, MLV (ref. 12). Here we present evidence that the latter effect is accompanied by a reduction in the detectable levels of circulating neutralizing antibody to MLV, and in particular by the absence of IgG neutralizing antibody.

Three groups of fifteen Balb/c female mice aged 9 weeks were infected with *Plasmodium berghei yoelii* (Pby) only, MLV alone, or both agents together, as previously described¹²; a fourth group was untreated. The onset of lymphoma is illustrated in Fig. 1. All surviving mice were bled at intervals from 2.5 weeks to 28 weeks after infection, and pooled sera from each group were tested for virus-neutralizing activity (Fig. 2) by inhibition of focus formation by the MLV pseudotype of the Harvey strain of murine sarcoma virus MSV (MLV) (ref. 13). In the group infected with MLV and Pby the neutrali-

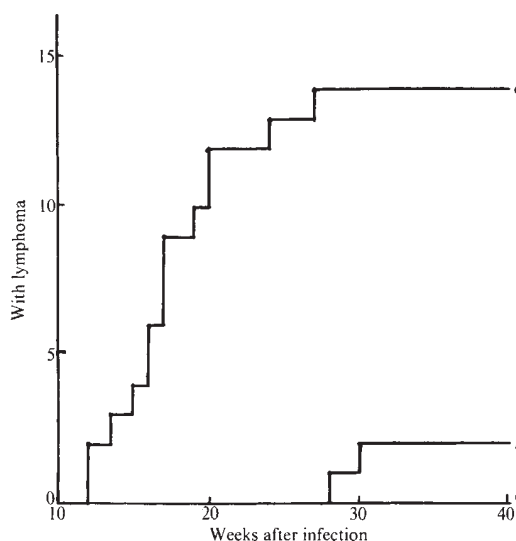


Fig. 1 The number of mice developing lymphoma after infection with MLV alone or MLV and Pby. a, Pby alone (0/15); b, MLV only (2/15); c, Pby+MLV (14/15).

zing antibody response 3.5 weeks after infection did not differ from that of mice infected with MLV alone, but thereafter remained consistently lower. Also included in Fig. 2 are neutralizing antibody levels from a group of mice infected with MLV as neonates. Eight weeks after infection the level of antibody observed in these animals was similar to that in mice infected with Pby and MLV as adults, but at 10 weeks the mice that had been inoculated neonatally became leukaemic and antibody was no longer detectable in their sera. Neutralizing activity had also disappeared from the sera, taken at 12 weeks, of individual leukaemic mice from the group infected

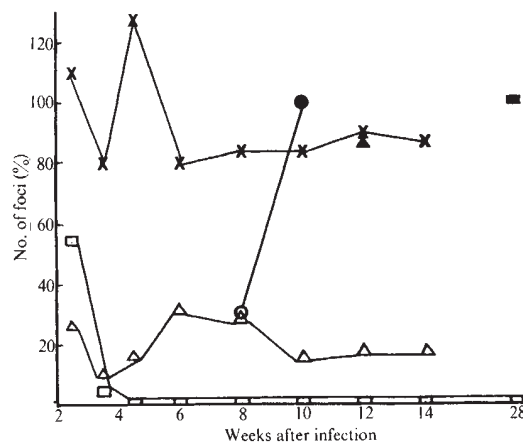
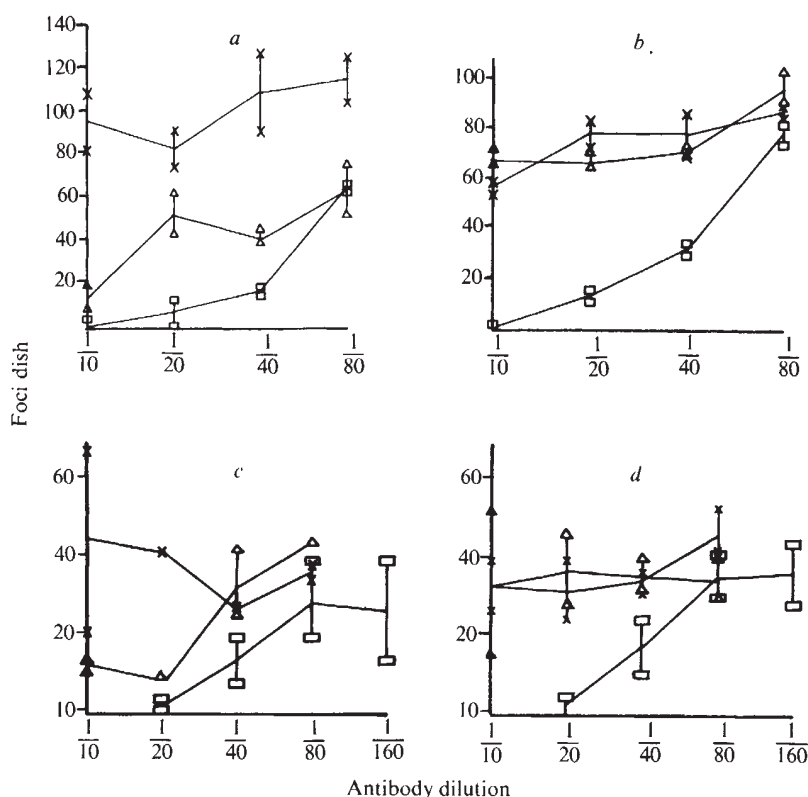


Fig. 2 Percentage reduction of focus formation by MSV (MLV) by sera from Balb/c mice. x, Infected with Pby alone; □, with MLV alone; △, with both MLV and Pby; ●, with MLV alone as newborns. ■, ▲, ●, Sera from leukaemic mice. In each test 0.02 ml. of heat inactivated (56° C, 30 min) serum was added to 0.18 ml. of a pool of the Harvey strain of MSV containing about 100 focus forming units. The mixture was incubated at room temperature for 90 min, 3.4 ml. of medium (Dulbecco's modification of Eagle's medium with 5% heat-inactivated calf serum) was added and 1.2 ml. aliquots were transferred to each of three 50 mm Nunclon dishes seeded the previous day with 2×10^5 Balb/c 3T3 cells (on which focus formation of MSV follows one-hit kinetics)¹³ and treated with 5 ml. of DEAE-dextran²² at 30 µg ml.⁻¹ in phosphate-buffered saline for 1 h at room temperature immediately before infection. The dishes were incubated at 37° C. One day later 4 ml. of medium were added. Seven days after infection the dishes were stained (Giemsa) and foci counted.

Fig. 3 Titration of sera from Balb/c mice at 6 weeks after infection (*a* and *b*) and at 10 weeks (*c* and *d*). With 2ME treatment (*b* and *d*) or without (*a* and *c*). Sera were mixed with an equal volume of saline, or saline containing 0.2 M 2ME, left for 1 h at room temperature and dialysed overnight at 4° C against 400 ml. of saline. ×, Uninfected mice; ■, MLV only; △, MLV + Pby. The vertical lines indicate the variation of focus number between two replicate dishes.



as adults with both agents, and from the serum, taken at 28 weeks, of one mouse infected with MLV only, as indicated by the solid symbols in Fig. 2.

The lack of effect of Pby infection on the early antibody response to MLV and its subsequent inhibitory effects, together with the fact that the IgG response to sheep erythrocytes is depressed more severely than the IgM (H. S. Micklem, personal communication) suggested that Pby infection might selectively inhibit the IgG response to the virus. Also it has been proposed that the IgG response to MLV is absent in neonatally-infected mice, where infectious circulating immune complexes have been found, neutralizable by anti-IgM but not by anti-IgG antibody¹⁴.

Aliquots of sera from untreated, MLV infected, and Pby + MLV infected mice taken at 6 and 10 weeks after infection were treated with 2-mercaptoethanol (2ME) and neutralizing activity titrated (Fig. 3). At both 6 and 10 weeks the activity of sera from mice infected with both agents was abolished by 2ME; serum from mice infected with MLV alone was partly resistant at 6 weeks and completely resistant at 10 weeks.

The absence of measurable virus-neutralizing IgG in doubly infected mice does not necessarily mean that no such antibody is produced; we cannot exclude the possibility that the IgG is being selectively adsorbed out by virus antigens, or rapidly catabolized as a consequence of overall raised IgG levels after malarial infection^{15,16}. But the absence of IgG could be accounted for if malarial infection were specifically preventing T (thymus-derived) lymphocytes from responding to MLV, because for several antigens it has been shown that the IgG response is more T cell-dependent than the IgM response^{17,18}.

The depressed humoral response to MLV in dually-infected mice could contribute to the enhancement of lymphomagenesis. The importance of antibody in controlling lymphomagenesis by MLV has been demonstrated by conferring protection in passive antibody transfer experiments¹⁹. ALS treatment enhances lymphomagenesis by MLV (ref. 20), and reduces the levels of detectable circulating neutralizing antibody²¹. We cannot judge whether the absence of IgG could be of particular significance in allowing malignant cells to escape immune attack.

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- Salaman, M. H., Wedderburn, N., and Bruce-Chwatt, L. J., *J. Gen. Microbiol.*, **59**, 383 (1969).
- Greenwood, B. M., Playfair, J. H. L., and Torrigiani, G., *Clin. Exp. Immunol.*, **8**, 467 (1971).
- Greenwood, B. M., Brown, J. C., de Jesus, D. G., and Holborrow, E. J., *Clin. Exp. Immunol.*, **9**, 345 (1971).
- Barker, L. R., *J. Inf. Dis.*, **123**, 99 (1971).
- Sengers, R. C. A., Jerusalem, C. R., and Doesburg, W. H., *Exp. Parasitol.*, **30**, 41 (1971).
- Congdon, L. L., and Wescott, R. B., *Lab. Animal Sci.*, **22**, 242 (1972).
- McGregor, I. A., and Barr, M., *Trans. Roy. Soc. Trop. Med. Hyg.*, **36**, 364 (1962).
- Greenwood, B. M., Bradley Moore, A. M., Palit, A., and Bryceon, A. D. M., *Lancet*, **i**, 169 (1972).
- Salaman, M. H., *Proc. Roy. Soc. Med.*, **63**, 11 (1970).
- Burkitt, D. P., *J. Nat. Cancer Inst.*, **42**, 19 (1969).
- Jerusalem, C., *Z. Tropenmed. Parasit.*, **19**, 94 (1968).
- Wedderburn, N., *Lancet*, **ii**, 1114 (1970).
- Aaronson, S. A., Jainchill, J. L., and Todaro, G. J., *Proc. US Nat. Acad. Sci.*, **66**, 1236 (1970).
- Branca, M., de Petris, S., Allison, A. C., Harvey, J. J., and Hirsch, M. S., *Clin. Exp. Immunol.*, **9**, 853 (1971).
- Fahey, J. L., and Robinson, A. G., *J. Exp. Med.*, **118**, 845 (1963).
- Smithers, S. R., in *Immunological Aspects of Parasitic Infections* (edit. by Bier, O.), *WHO Scientific Publ.*, **150**, 43 (Pan-American Health Org., 1967).
- Taylor, R. B., and Wortis, H. H., *Nature*, **220**, 927 (1968).
- Munro, A. J., and Hunter, P., *Immunol.*, **23**, 69 (1972).
- Klein, E., and Klein, G., *J. Nat. Cancer Inst.*, **32**, 547 (1964).
- Allison, A. C., and Law, L. W., *Proc. Soc. Exp. Biol. Med.*, **127**, 207 (1968).

²¹ Law, L. W., and Chang, S. A., *Proc. Soc. Exp. Biol. Med.*, **163**, 420 (1971).

²² Duc-Nguyen, H., *J. Virol.*, **2**, 643 (1968).

A Critique of McClare's Quantum Mechanical Muscle Model

THE explanation of muscle contraction by McClare^{1,2} is at variance with the current tenets of molecular spectroscopy. Lifetime measurements have shown that, in most cases, the excimer has a shorter half-life than that of the parent monomer³. In pyrene, the example quoted by McClare, the half-life (at room temperature) of the monomer is 31×10^{-8} s, while that of the excimer is only 4.4×10^{-8} s.

Azumi and McGlynn⁴ observed an excimer emission from solid solutions of pyrene with a lifetime of 10^{-2} s, which they attributed to "an inherent forbidden character of excimer fluorescence itself". It was later found⁵ that their delayed fluorescence arose from an excimer produced by triplet-triplet annihilation; that is, the emission owed its longevity to the delay in the production of the emitting species and not to its slow decay.

I have shown⁶ that two molecules in the lowest triplet state will not interact to yield an excited singlet species (monomer or excimer) if they are situated 3.0 nm apart. Thus McClare's oscillators, even if they are postulated to be in the first excited triplet state, would not interact and come closer. If the initial distance is changed to 1.0 nm, electron exchange interaction leading first to an excited singlet monomer and later to an excimer will occur; but then the excimer will not be long-lived.

If the excimer has a centre of symmetry, excimer fluorescence will be dipole-forbidden⁷. Experimental evidence, however, suggests that random thermal motion of the two monomers can lower the symmetry and make the transition dipole-allowed. In a rigid matrix, a symmetrical excimer, once formed, will be unable to radiate; but in such a matrix the two oscillators will be prevented from coming closer and McClare's model would fail.

McClare also presents the analogy of the lowest triplet state of chrysene which can be stabilized for as long as a second, and argues that an excimer could also be similarly stabilized. Although the radiative transition of a symmetrical excimer is dipole-forbidden, as is the phosphorescence from the triplet state of an organic molecule, there is an essential difference between the two species. The first triplet state is the lowest excited state of the molecule, but the singlet excimer state is not; the excimer can always decay by crossing over to its (lower lying) triplet state. Hence a symmetrical excimer cannot be stabilized for as long as the lowest triplet state of an organic molecule.

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¹ McClare, C. W. F., *Nature*, **240**, 88 (1972).

² McClare, C. W. F., *J. Theor. Biol.*, **35**, 569 (1972).

³ Birks, J. B., in *Photophysics of Aromatic Molecules*, 351 (John Wiley, New York, 1970).

⁴ Azumi, T., and McGlynn, S. P., *J. Chem. Phys.*, **39**, 3533 (1963).

⁵ Smith, F. J., and McGlynn, S. P., *J. Chem. Phys.*, **42**, 4308 (1965).

⁶ Razi Naqvi, K., *Chem. Phys. Lett.*, **1**, 497 (1967).

⁷ Hoijtink, G. J., *Z. Elektrochem.*, **64**, 156 (1960).

McClare's Quantum Mechanical Muscle Model

STARTING from the belief that the "energy" for muscular contraction is derived from the "energy" released by the hydrolysis of ATP, McClare¹ has concluded that this "energy" must initially be stored in individual molecules of ATP. The amount of "energy" so stored is supposed to equal the enthalpy

change for the hydrolysis of ATP (presumably in its ground state), at pH 7.4. A considerable part of the quoted figure (-40 kJ mol^{-1}) is, in fact, due to the heat of neutralization of a proton which is formed in near stoichiometric amount at this pH (refs. 2, 3). Nevertheless, McClare proposes that the total enthalpy change is somehow trapped in the other two products of hydrolysis, ADP and inorganic phosphate, which subsequently exist in an excited "state", out of thermal equilibrium with surrounding molecules for a significant time. A calculation then shows that the wavelength of radiation having energy equivalent to this enthalpy change is $3 \text{ }\mu\text{m}$, which lies in the infrared. McClare concludes from this that the "energy" is stored (in ADP and inorganic phosphate) in a vibrational mode. The lifetime of a vibrational excited state is quoted as being *ca.* 10^{-7} s.

But this figure is typical only for dilute gases of small molecules (2 to 6 atom at 10^{-2} – 10^{-3} atm) where the lifetime is collisionally limited. At much lower pressures (for example, in outer space), the lifetime of a single vibrationally excited molecule is its radiative lifetime, which for ordinary molecules is of the order of 10^{-4} s. Under such conditions, the excited energy-level is sharp, with a linewidth of about $5 \times 10^{-8} \text{ cm}^{-1}$. In aqueous media, on the other hand, vibrational energy-levels as revealed by infrared absorption bands are rather broad (typically $\Delta\nu = 100 \text{ cm}^{-1}$) and the lifetimes of the vibrational excited "states" are correspondingly smaller, by perhaps about 10 orders of magnitude. This may be simply seen as follows. In a condensed phase, initially formed vibrational excited "states" are coupled intra- and intermolecularly (by "resonant transfer" in McClare's terminology) to a quasi-continuum of other vibrational "states". A quantum-mechanical treatment of uniform coupling⁴⁻⁷ gives the first order decay lifetime of an initially excited zeroth-order "state" as $\tau = 5.3 \times 10^{-12} \times (\Delta\nu)^{-1} \text{ s}$ ($\tau \times \Delta\nu = \hbar/hc$). With $\Delta\nu = 100 \text{ cm}^{-1}$, $\tau = 5 \times 10^{-14} \text{ s}$; that is, 6 or 7 orders of magnitude less than the figure given by McClare. Another indication of such short vibrational lifetimes comes from, for example, the feasibility of dye lasers which otherwise would not work.

This means that for all practical purposes vibrational energies of molecules in aqueous solution are accurately distributed according to the Boltzmann Law, that is, they are thermally equilibrated. It is not possible to isolate a vibrational mode from thermal equilibrium for the time required by McClare. Even if the hydrolysis of ATP takes place on the surface of elements of the myofibril system and not in free solution the situation is unlikely to be very different. In any case, the value of the enthalpy-change would then be unknown and might well be close to zero if a proton were not produced in near stoichiometric amount.

McClare is led to "restate" the second law because of his initial premise that ATP can store and provide "energy" while remaining in steady state. The model for muscle contraction which follows requires the isolation of a particular vibrational mode from thermal equilibrium in a condensed phase, and this is not physically possible—unless, of course, Maxwell's Demon intervenes. We note that he has accused a number of muscle physiologists of invoking the assistance of this particular entity.

There can be little doubt that the behaviour of biological systems conforms to the laws of classical thermodynamics as usually understood. There is in principle no particular difficulty in calculating the value of the change in Gibbs function for a muscle contraction providing that the concentrations of all those chemical species which show a net change in amount can be measured before and after contraction. In practice this is obviously technically difficult. But no one has reported a positive value for the change in Gibbs function in these circumstances and until they do we can continue to believe that muscle contraction conforms to the second law.

Were the opening sentence of McClare's article true, that is, if the physiology, biochemistry and structure of muscle were now well understood, there would be no need for models at all. The fact is that the molecular events associated with muscle

contraction are not yet understood. While it is obviously important that, until they are, models should be proposed and considered, we conclude that the one put forward by McClare has nothing particularly to do with quantum mechanics or thermodynamics or muscle contraction.

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¹ McClare, C. W. F., *Nature*, **240**, 88 (1972).

² George, P., and Rutman, R. J., *Progr. Biophys.*, **10**, 2 (1960).

³ Phillips, R. C., George, P., and Rutman, R. J., *J. Biol. Chem.*, **244**, 3330 (1969).

⁴ Zener, C., *Proc. Roy. Soc., A*, **137**, 696 (1932).

⁵ Landau, L. D., and Lifshits, E. M., *Quantum Mechanics*, 325 (Pergamon, 1965).

⁶ Robinson, G. W., and Frosch, R. P., *J. Chem. Phys.*, **38**, 1187 (1963).

⁷ Bixon, M., and Jortner, J., *J. Chem. Phys.*, **48**, 715 (1968).

Hyperfiltration Streaming Potential as a Probe of Water Structure in Membranes

ONE of the most important problems in the physical chemistry of biological systems involves the question of water structure in the vicinity of a charged surface, such as a polyelectrolyte membrane. In a recent review of water structure in biological systems, Dröst-Hansen¹ has contended that a wide variety of data²⁻⁴ point to the existence of transitions in water structure at 15° C, 32° C and 45° C, if the water is in contact with a structuring interface. We present further evidence to support the existence of a transition in the vicinity of 32°–40° C.

We have previously demonstrated that measurements of streaming potential on polyelectrolyte membranes as a function of pressure during a hyperfiltration experiment⁵ yield the electro-osmotic coefficient, β . This coefficient directly measures the association between the counter-ions and the water in the membrane, and it therefore seems reasonable to believe that it should be quite sensitive to any change in water structure as a function of temperature.

Reports^{6,7} of electro-osmotic experiments at various temperatures have found that the electro-osmotic coefficient tends to decrease with increasing temperature. However, McHardy *et al.*⁸ studied 'Zeo-Karb 315', a commercial cation exchanger, from 15° C to 35° C and found no variation (all results within 2% of one another). The choice of temperature range will be shown to be unfortunate, although the results are in agreement with those observed in the present communication.

In Fig. 1, measurements of the streaming potential at various temperatures are shown as a function of the effective pressure⁵ (which to a first approximation is the pressure applied). All the measurements were performed on Collodion/polyvinylamine anion exchange membranes using 10⁻² N KCl feed solutions as previously described⁹, in which the temperature was controlled to $\pm 0.1^\circ$ C. The slope of the plots in Fig. 1 is the electro-osmotic coefficient, β , and this parameter declines substantially as the temperature is raised. When β is plotted as a function of temperature (Fig. 2), it becomes clear that the onset of a precipitous decline begins in the vicinity 35°–36° C. As mentioned earlier, the present results agree with those of

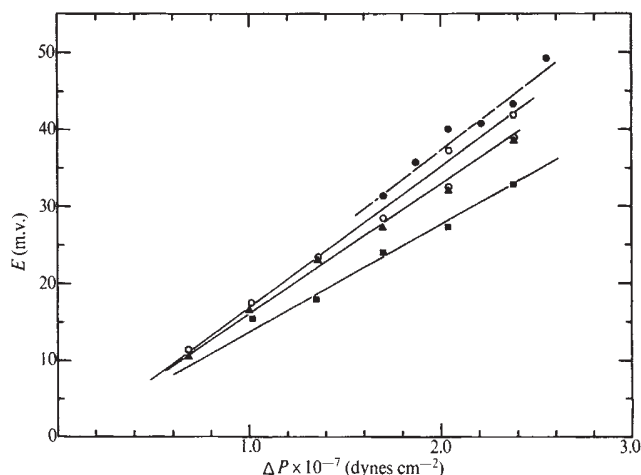


Fig. 1 Streaming potential of membrane PVA-1 as a function of applied pressure at a number of temperatures. All potentials have been corrected for the effect of pressure on the Ag/Ag Cl electrodes. ●, 291 K; ○, 308 K; ▲, 313 K; ■, 318 K.

McHardy *et al.*⁸, in that β does not change by more than about 2% in the plateau region of 15°–35° C in Fig. 2.

One must now consider whether factors other than a change in water structure could produce the effect on β observed in Fig. 2. We have previously derived⁵ an equation which was shown to correctly predict the concentration dependence of the electro-osmotic coefficient,

$$\beta = \frac{\phi_w}{X + \frac{f_{wm}\bar{c}_w}{f_{1w}} \left(1 + \frac{\bar{c}_s}{t_1 X} \right)} \quad (1)$$

where ϕ_w is the fractional membrane water content, X the effective charge density, f_{wm} , f_{1w} the water/membrane and anion/water frictions respectively, $\bar{c}_s$, $\bar{c}_w$ the salt and water concentrations respectively within the membrane, and t_1 is the counter-ion transport number, taken as the ratio of the counter-ion mobility to that of the salt.

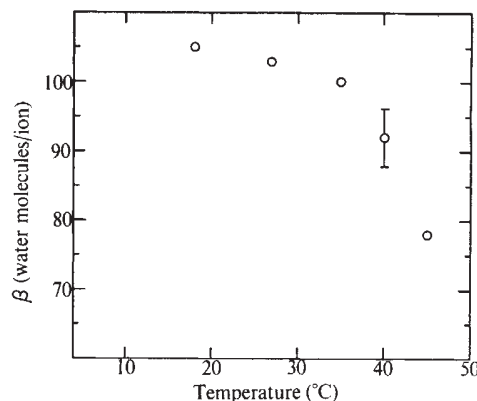


Fig. 2 The electro-osmotic coefficient as a function of temperature.

Inspection of the parameters in equation (1) reveals that either a decrease in ϕ_w or an increase in $\bar{c}_s$ would cause β to decline. One of the advantages of the method is that the limiting salt rejection, R_∞ , can be measured simultaneously, and this may be used as a monitor of $\bar{c}_s$ with temperature. If $\bar{c}_s$ were to increase, one would expect R_∞ to decline. In Table 1, measurements of R_∞ and ϕ_w are shown at various temperatures,

and both may be seen to remain constant or perhaps increase slightly. Thus, it seems reasonable to suggest that the weak de-coupling of the outer water associated with the ion (Fig. 2) is associated with a minor change in the water structure within the membrane.

Table 1 Measurements of R_{∞} and ϕ_w at Various Temperatures

Temperature	Rejection (%)	ϕ_w
25° C	58.5	0.54
30	60.5	—
35	60.0	—
40	60.0	—
45	—	0.59

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¹ Drost-Hansen, W., in *Chemistry of the Cell Interface, Part B*. (edit. by Brown, H. D) (Academic Press, London and New York, 1971).

² Peschel, G., and Aldinger, K. H., *Naturwissenschaften*, **54**, 614 (1967).

³ Forslind, E., *Sv. Naturvetenskap*, **2**, 9 (1966).

⁴ Dreyer, G., Kahrig, E., Kirstein, D., Eppenbeck, J., and Lange, F., *Naturwissenschaften*, **56**, 558 (1969).

⁵ Tanny, G., and Hoffer, E., *J. Coll. and Int. Sci.* (in the press).

⁶ George, J. H. B., and Courant, R. A., *J. Phys. Chem.*, **71**, 246 (1967).

⁷ Arnold, R., *J. Phys. Chem.*, **73**, 144 (1969).

⁸ McHardy, W. J., Meares, P., Sutton, A. H., and Thain, J. F., *J. Coll. and Int. Sci.*, **29**, 116 (1969).

⁹ Tanny, G., Hoffer, E., and Kedem, O., *Experimental Suppl.*, **18**, 619 (1971).

Parthenogenesis in the Mouse

In vitro treatment of mouse eggs with hyaluronidase can activate them to develop parthenogenetically as well as denuding them of cumulus cells¹⁻⁴. Activation and subsequent behaviour of the eggs depend on certain defined conditions. Szollosi⁵ observed morphological changes in unfertilized mouse eggs *in vivo* after approximately 14 h in the oviduct. Rotation and migration of the spindle towards the centre of the egg was the first and most obvious change. This prepares the egg for equal cleavage rather than the usual unequal division which results in the formation of the second polar body. Graham⁶ stimulated eggs 12–17 h after ovulation and obtained about 30% “immediate cleavage”⁸ in the activated group, whereas Tarkowski^{7,8} applied an electric shock to the exposed oviduct 2–4 h after ovulation and obtained activation in approximately 50% but a very low incidence of immediate cleavage. This suggested that the time of activation after ovulation might be important in the type of parthenogenones induced. Eggs were considered to have undergone immediate cleavage only if, at the time of examination, they were morphologically indistinguishable from a normal fertilized two-cell egg—that is, apart from the absence of a second polar body. They resulted from a biochemical or experimental stimulus other than that provided by fertilization. The few eggs with unequal blastomeres were therefore not included in this group.

(C57Bl × A₂G)F₁ females were superovulated and killed at intervals of 2 h, 14–20 h after injection of human chorionic gonadotrophin (HCG). (Ovulation occurs approximately 12 h after this injection.) Oocytes were released from the ampullae into a modified Krebs-Ringer bicarbonate culture medium containing 4 mg ml.⁻¹ bovine serum albumin⁹ and 100 IU ml.⁻¹ hyaluronidase (Koch-Light, ovine testes), and incubated at 37° C in 5% CO₂ in air. After 10 min the eggs were transferred to a hyaluronidase-free medium and culture continued for a further 6 h. Atretic and fragmented eggs were not transferred to the hyaluronidase-free medium as they were ovulated in this state, or resulting from the PMSG-induced ovulation¹⁰.

Eggs were examined under the ×50 magnification of a Wild dissecting microscope to determine the overall frequency and types of parthenogenones induced. These results are presented in Table 1 (groups 1 to 4). Results from a more extensive series in which mice were autopsied 18–20 h after injection of HCG are also presented in Table 1 (group 5). If the results of groups 1 to 5 are combined, 740/757 (97.8%) of the activated eggs had a single pronucleus and second polar body (the first very rarely persists), seven had two pronuclei (0.9%) and ten underwent immediate cleavage (1.3%). Further groups of mice were killed approximately 25 h after HCG and these results are presented in Table 1 (groups 6 and 7). Control eggs were cultured in hyaluronidase-free medium. No spontaneous activation was observed at the time of isolation of the eggs from the oviducts and only in the more aged groups was handling of the eggs sufficient to activate a proportion of the eggs in the control series. In the group 6 (where a fresh epididymal sperm suspension in the modified Krebs-Ringer bicarbonate culture medium described earlier was used as the stimulus) the overall frequency of activation was 73.2% (224/306), but the incidence of the various types of parthenogenones differed considerably from the previous series, with immediate cleavage in 77.7% (174/224). In group 7 (where hyaluronidase medium was used) a similar frequency of activation was obtained (75.4%, 288/382) and a slightly lower incidence of immediate cleavage (62.2%, 179/288).

These results place on a quantitative basis the ageing changes previously observed⁵, and probably explain the high incidence of immediate cleavage observed in late insemination by Marston and Chang¹¹. This seems to be a more likely explanation than that spindle migration occurred as a direct result of the activation procedure as suggested by Braden and Austin⁶, though this central migration might be accelerated by heat^{6,12} or other experimental stimuli⁷. A low incidence of eggs with two haploid sets of chromosomes without extrusion of the second polar body was observed in this series. This may be explained by strain variation¹³.

In another series of experiments where females were killed approximately 20 h after injection of HCG and eggs were added to a fresh epididymal sperm suspension (group 8), 774/1404 eggs were activated (55.1% overall activation frequency). The frequency of activation was 62.8% (558/888) when similar eggs were added to a sperm-free filtrate (group 9). When aged eggs were added to a sperm suspension (groups 6 and 8), certain factors in the suspension activated the eggs mechanically or biochemically. By filtering the sperm suspension through a ‘Millipore’ filter (group 9) I concluded that activation is not due to direct (mechanical) stimulation by sperm, but to a factor or factors released by sperm into the culture medium (for example hyaluronidase or other enzymes from the acrosomal region).

My results help to define the conditions needed for the experimental induction of different types of parthenogenones. The critical factor is clearly the age of the oocyte when the stimulus is applied.

Varying the osmolality of the culture medium also results in different types of parthenogenone^{3,4}, an effect that may possibly arise through changes resembling those that accompany ageing.

I thank Professor C. R. Austin for his criticism of the manu-

Table 1 Reaction of Eggs 6 h after Addition to Various Experimental Situations

Group	Stimulating medium	Hours after HCG injection when females were killed	Total number of eggs	Activated eggs 1 pronucleus + 2nd polar body	2 pronuclei	Immediate cleavage	Overall % activation
1.	Hyaluronidase medium	14	172	—	—	—	0.0%
2.	Hyaluronidase medium	16	211	56	1	—	27.0%
3.	Hyaluronidase medium	18	117	89	—	—	76.1%
4.	Hyaluronidase medium	20	137	112	2	1	83.9%
5.	Hyaluronidase medium	18–21	689	483	4	9	72.0%
6.	Fresh sperm suspension	25	306*	50 (combined group)		174	73.2%
7.	Hyaluronidase medium	25	382*	96	13	179	75.4%
8.	Fresh sperm suspension (a)	18–20	1,404	756	34†	18	55.1%
9.	Sperm-free filtrate of (a)	18–20	888	537	9	12	62.8%

* Apparently normal one-cell eggs or immediately cleaved eggs as observed 6 h after addition to the stimulating medium. About 5% of eggs transferred to the hyaluronidase medium (and controls) in the 25 h group were fragmented at 6 h, and these are excluded from the total of group 7 to make the data comparable with those from group 6. No fragmentation was seen at 6 h after activation in the other time groups or in their controls.

† Possibly due to *in vitro* fertilization, so these eggs are not included in calculation of activation frequency.

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- ¹ Graham, C. F., *Symp. Wistar Inst.*, No. 9, 19 (1969).
- ² Graham, C. F., *Nature*, **226**, 165 (1970).
- ³ Graham, C. F., *Adv. Biosci.*, **6**, 87 (1971).
- ⁴ Graham, C. F., *Adv. Biosci.*, **8**, 263 (1972).
- ⁵ Szollosi, D., *Amer. J. Anat.*, **130**, 209 (1971).
- ⁶ Braden, A. W. H., and Austin, C. R., *Exp. Cell Res.*, **7**, 277 (1954).
- ⁷ Tarkowski, A. K., *J. Reprod. Fert.*, Suppl., **14**, 31 (1971).
- ⁸ Tarkowski, A. K., Witkowska, A., and Nowicka, J., *Nature*, **226**, 162 (1970).
- ⁹ Whittingham, D. G., *J. Reprod. Fert.*, Suppl., **14**, 7 (1971).
- ¹⁰ Fowler, R. E., and Edwards, R. G., *J. Endocrin.*, **15**, 374 (1957).
- ¹¹ Marston, J. H., and Chang, M. C., *J. Exp. Zool.*, **155**, 237 (1964).
- ¹² Fankhauser, G., and Godwin, D., *Proc. US Nat. Acad. Sci.*, **34**, 544 (1948).
- ¹³ Braden, A. W. H., *J. Genetics*, **55**, 476 (1957).

Sexual Behaviour and Sexual Motivation in the Female Rat

Is the sexual behaviour of the female rat pure reflex, or does oestrus also stimulate active efforts to approach the male? Male rats will learn to run an alley if rewarded with an oestrous female, and their performance in the alley is then controlled by the same hormone that controls the mating acts, testosterone¹. Attempts have been made to train female rats to learn an alley in which the reward was a copulating male, but they did not learn to run any faster than others rewarded with an impotent male (and no copulation) (refs. 2 and 3, and M. Williams

and R. F. D., unpublished results). The control females, however, learned very rapidly to run to an impotent male; and it is possible, therefore, that the effects of this (presumably social) reward are so strong as to mask any additional, specifically sexual, reward that mating itself may provide. In the experiment reported here, the choice of an individual female for a potent (copulating) as against an impotent male was examined, using a T-maze.

The animals used were eight young Wistar females, and ten Wistar males preselected for good sexual performance. Under 'Nembutal' anaesthesia 50% of males were castrated and the females ovariectomized. Oestrus was reinstated in the females as required with injections of oestradiol (5 µg given subcutaneously in arachis oil, 48 and 24 h before the test) and progesterone (400 µg given subcutaneously in arachis oil or propylene glycol 8 h before the test). Training took place in a wooden T-maze 25 cm high. The stem measured 27.5 by 30 cm and the two arms were each 27.5 by 39 cm; all three were fitted with opaque sliding doors 15 cm from the end, raised by a string equipped with counter-weights.

At the start of each trial the female rat was placed behind the door in the stem. A potent male was positioned behind the door of one arm, and an impotent male behind the door of the other; which male was in which of the arms for each female was fixed on her first trial by the toss of a coin: thereafter it remained unchanged. To start each trial, the female was released from her compartment in the maze. When she had moved into one of the two arms of the maze (with her whole body excluding the tail), the male in that arm of the maze was released. The choice and its latency were recorded. The chosen male and the female were left together for a standard interval. This was 2 min during the first trials, but was subsequently reduced to 1 min because mating was reliably obtained in the shorter interval. The duration of access to the potent and the impotent male were thus identical, the only difference being in what they did to the female.

After any trial in which a potent male ejaculated, he was replaced with another from the stock of five; and the impotent male was also changed, so as to equate their novelty. During a

training session trials followed one another without a break. As a rule eight trials were given in each session, though this was not invariable. The sessions were separated by an interval of at least 4 days. The criterion for successful training was eight consecutive turns towards the potent male.

During this part of the experiment the females received an average of 3.5 intromissions during each minute spent with the potent male, and one ejaculation every 2.7 min. The castrated males showed no sexual behaviour other than occasional desultory mounts. All eight females learned to choose the potent male to the criterion, in a mean of 32.2 trials (standard deviation 15.3). Using this criterion, a "criterion risk" (that is the risk of a criterion being reached, given random performance) of 5% is exceeded if more than thirty-one trials are run⁴. To ensure that the criterion had not been reached by chance, the position of the males was reversed for each female as soon as she reached the criterion, and she was then retrained to the same criterion in the same way. All eight animals relearned the task to criterion, in an average of 86.4 trials (s.d. 32.8). The learning curve for this part of the experiment is shown as Fig. 1. This curve illustrates the progressive learning shown by the females. It is clear that attainment of the criterion is the outcome of this gradual learning process, and not a chance effect. It should also be noted that the rats trained in this experiment showed a classic negative transfer, taking twice as long to learn the second as the first response.

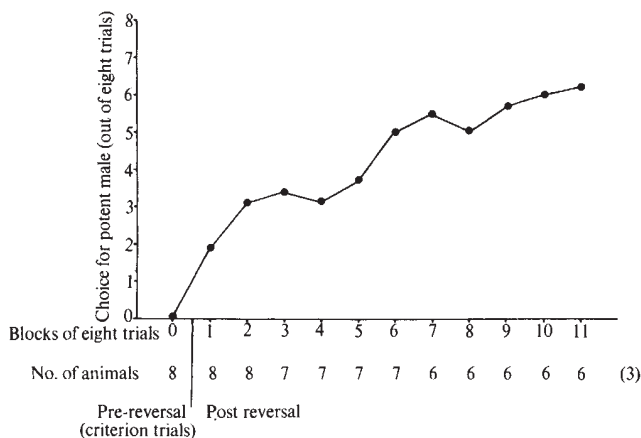


Fig. 1 Choice for a potent, as against an impotent, male by the female rat. This figure shows the course of learning when the position of the males is reversed following original training. The results from an animal are only included in the figure up as far as the end of the eight trials on which criterion was reached. By the eighty-eighth trial most of the animals had reached criterion, and the curve is therefore not continued beyond this trial.

When all the animals had reached criterion, the hormonal determinants of this learned approach to the male were examined. Six of the eight animals were run in the maze in the same way for a further period, in blocks of twelve trials given at weekly intervals. But interspersed among these "oestrous" blocks were blocks of trials similar in every way except that the females were not pretreated with hormones and hence were not sexually receptive. In all 204 "oestrous" trials and 108 "unreceptive" trials were run.

The absence of behavioural oestrus neither reduced the females' preference for the potent males nor increased the latency of the choice. During the 204 trials on which the females were sexually receptive, they chose the potent male on 73%, with an average latency of 4.4 s; on the 108 trials without hormone treatment they chose the potent male on 80% of the trials with an average latency of 2.6 s. On none of the "unreceptive" trials did they show any indications of lordosis. Altogether, then, these findings give no indication that oestrus

involves the stimulation of any behaviour more complex than the unlearned motor patterns characteristically associated with it.

Oestrus is associated with enhanced general activity⁵, but seems to be independent of sexual receptivity. Progesterone, which synergizes with oestrogen to enhance sexual receptivity, does not increase such activity^{6,7}; and differentiation as a normal male, which virtually eliminates female sexual responsiveness to oestrogens, does not prevent the greatly increased activity that results from ovarian implants⁸. The hyperactivity of oestrus, therefore, does not betoken an effort to seek out a male with which to mate because (1) it can be dissociated from sexual receptivity under several conditions and (2) approach behaviour directed to the male is found to be uninfluenced by ovarian hormones that suffice to produce sexual receptivity, when examined directly.

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¹ Beach, F. A., and Jordan, L., *J. Comp. Physiol. Psychol.*, **49**, 105 (1956).

² Bolles, R. C., Rapp, H. M., and White, G. C., *J. Comp. Physiol. Psychol.*, **65**, 311 (1968).

³ Beach, F. A., in *Biological and Biochemical Bases of Behaviour* (edit. by Harlow, H. F., and Woolsey, C. N.) (University of Wisconsin Press, Madison, 1958).

⁴ Bogarts, R. S., *Psychol. Bull.*, **64**, 1 (1965).

⁵ Wang, G. H., *Comp. Psychol. Monogr.*, **2**, 1 (1923).

⁶ Young, W. C., and Fish, W. R., *Endocrinology*, **36**, 181 (1945).

⁷ Kennedy, G. C., *J. Physiol.*, **172**, 383 (1964).

⁸ Wang, G. H., Richter, C. P., and Guttmacher, A. F., *Amer. J. Physiol.*, **73**, 581 (1925).

Orientation-sensitive After-effects of Dichoptically Presented Colour and Form

McCOLLOUGH¹ discovered that if a grating pattern of (say) red vertical stripes is viewed alternately with one of green horizontal stripes for some minutes, an orientation-specific colour after-effect is observed when viewing a black-and-white test grating. White stripes in a given orientation appear tinted with the hue complementary to the hue presented at that orientation in the original stimulus. McCollough observed that if only one eye was exposed to the original sequence of stimuli, no after-effect was seen when the other eye was used to view the test grating. From this she concluded that the adaptation responsible for the after-effect must occur somewhere in the uniocular pathway before signals from left and right eyes are combined. She suggested as a possible explanation that orientation-sensitive channels in the uniocular nervous system ("edge-detectors") may be colour-coded, so that strong adaptation with bars of red light in one orientation leads to a "minus-red" after-response from the adapted channels to similarly oriented colourless bars. Harris and Gibson² have confirmed that the effect persists in conditions ruling out ordinary negative after-images, which Murch and Hirsch³ have shown sufficient to induce it. Held and Shattuck⁴ have demonstrated a corresponding after-effect of colour upon the perceived orientation of test bars.

In view of the reported absence of interocular transfer of this effect¹, the physiological locus of adaptation is of interest

as a clue to that of the presumed orientation-sensitive elements in the human visual system. Following a suggestion by Dr Stuart Butler of Birmingham (personal communication), we have investigated the after-effects of presenting information on colour and orientation separately to the two eyes, and have discovered a curious form of interaction between the two unicocular signals.

The subject sat in a darkened room and viewed with one eye a projection screen (2.15 metres away) on which orthogonal left-oblique and right-oblique black-and-white gratings (luminance 22 cd m^{-2} at centre of stripes) were presented alternately for equal periods of the order of 5–10 s, over a total period of 5 min. The patterns subtended $20^\circ \times 14^\circ$ and had a spatial frequency of 2.2 cycles/degree at the observer's eye. (Oblique orientations were used to avoid any bias associated with horizontal and vertical.)

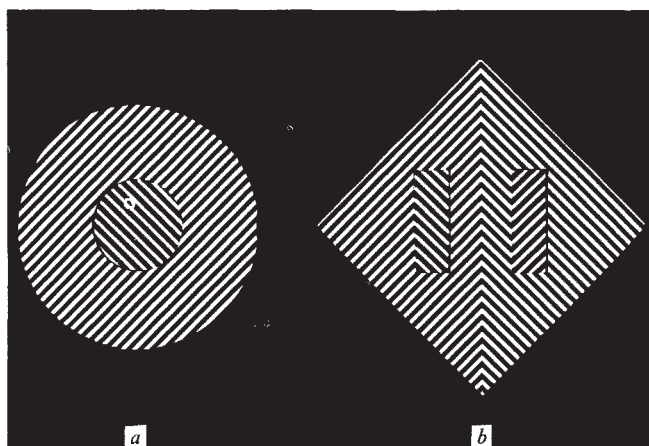


Fig. 1 Two of the test patterns used. The hue of the central patch(es) could be adjusted by the subject to match that of the background.

The subject's other eye was exposed to a uniformly illuminated diffusing screen whose colour changed from red to green as the striped patterns alternated. The visual subtense of the coloured field more than covered that of the striped patterns as viewed by the other eye. The luminances of red and green fields were matched at approximately 34 cd m^{-2} .

After 5 min of this dichoptic stimulation, subjects viewed a black-and-white test grating (2.2 cycles/degree) surrounded by an orthogonal black-and-white background grating of the same spatial frequency. Various shapes of test grating were used, the commonest being a disk subtending 4.5° degrees at the eye, at the centre of a circular background grating of 27 cd m^{-2} subtending 13.5° degrees (Fig. 1a). A later design which proved easier to use employed two oppositely oriented test patches side by side lying in oppositely oriented backgrounds (Fig. 1b). The two test orientations were always used alternately. As well as inviting verbal reports of perceived hue, we used a quantitative null-method of measuring the after-effect. The subject was provided with a (smooth-surfaced) knob by which the test patch could be made slightly red or green to neutralize its perceived hue. The luminance could be independently adjusted to match that of the background. The whole test field (patch plus background) could be rotated to give either orientation of the central test grating. As it turned out that many subjects had an initial bias whereby the test patch appeared greener or pinker than background according to slope even without prior stimulation, the measure adopted for the after-effect was the change in the bias

after adaptation. The bias itself was recorded as the difference between the readings for balance at the two orthogonal test orientations. We also verified that any after-effects of the faint colours imposed on the test patch during the matching process were too small to introduce a significant bias.

A detailed discussion of the results will be published elsewhere, but the most significant findings were as follows: (1) All subjects showed a significant orientation-sensitive colour after-effect of the dichoptic stimulation, most of them spontaneously reporting changes of hue from pink to green or vice-versa as the test grating was rotated through 90° . Subjects differed considerably in the precision with which they could reproduce a match, but in several cases there were significant signs of reversal of the after-effect after a few minutes, particularly in the eye that had received the coloured stimulus. (2) Quite unexpectedly, the initial after-effects in left (L) and right (R) eyes when tested singly were almost always in opposite directions. Table 1 shows a condensed summary of results obtained from nine subjects. As a check, all possible combinations of conditions were used (colours to L/R eye paired with patterns to R/L eye; each orientation paired with Red/Green; test field presented to L/R eye), though not all with every subject.

Table 1 Hues Seen when Viewing Black-and-White Test Grating with either Pattern-stimulated or Colour-stimulated Eye

		Subjects								
		V.M.	B.H.	S.J.	J.M.	E.M.	D.A.	R.M.	C.F.	D.M.
Hues seen with	S, S, S	S	S, S, S	S, S	S, S	S, S	S, S	S, S	S	S
pattern-stimu-	S, S		S, ?				S, ?	S, S		
lated eye										
Hues seen with	C, C, ?	C, C, C, ?	C, C	??	C, C	??	C, C	C	C	C
colour-stimu-	C, C	C, C					??	C, C		
lated eye										

S: Same as hue originally paired with similarly-oriented grating.
C: Complementary to hue originally paired with similarly-oriented grating. ? : Inconclusive result.

After allowing for initial bias, there were no consistent exceptions to the following summary: (a) Seen through the eye that originally received (colourless) patterned stimulation, a black-and-white test grating has the hue originally associated with the same orientation. The measured strength of this effect was found to be variable, and at most roughly half that of the normal McCollough effect. (b) Seen through the eye that originally received coloured but non-patterned stimulation, the test grating has (more weakly) the complementary hue to that originally associated with its orientation.

One possible inference from the results is that some transfer of information between L and R eye channels may be taking place before the stage at which form and colour are associated⁶; but whereas orientational information seems to be transferred correctly, it looks as if colour transfer is antagonistic—that is, as if (say) red light in one eye gives rise to a signal of “minus-red” in the other channel.

An obvious physiological question raised by these results is whether any colour sensitive units at the geniculate or other early stages of the primate visual pathway show signs of complementary sensitivity to colour in the other eye. Inhibitory interaction between pattern-evoked signals from the two eyes has frequently been found in the cat lateral geniculate nucleate^{6–8}. Alternatively, is there an efferent pathway whereby the neutral point of the red-green colour signalling system in both unicocular channels is centrally regulated?

We gratefully acknowledge the help of colleagues and

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¹ McCollough, C., *Science*, **149**, 1115 (1965).

² Harris, C. S., and Gibson, A. R., *Science*, **162**, 1506 (1968).

³ Murch, G. M., and Hirsch, Joy, *Amer. J. Psychol.*, **85**, 241 (1972).

⁴ Held, R., and Shattuck, S. R., *Science*, **174**, 314 (1971).

⁵ Creed, R. S., *J. Physiol.*, **127**, 381 (1935).

⁶ Suzuki, H., and Takahashi, M., *Brain Research*, **23**, 161 (1970).

⁷ Sanderson, K. J., Bishop, P. O., and Darian-Smith, I., *Exp. Brain Res.*, **13**, 178 (1971).

⁸ Noda, H., Tamaki, Y., and Iwama, K., *Brain Research*, **41**, 81 (1972).

Diurnal Variations of Water in Developing Secondary Stem Tissues of Eucalypt Trees

ZAHNER¹ has stated that living cambial tissues must be under moderate to severe water stress almost daily during the growing season because of the great tensile forces which develop in the adjacent mature xylem. We have studied diurnal water variations within the developing tissues of tree stems.

Samples were obtained by removing strips of bark from the stems of *E. regnans* trees and immediately scraping the exposed xylem and phloem surfaces. Each tissue sample was placed in a tared glass tube which was stoppered, weighed and partially immersed in a mixture of dry ice and ethanol. The samples were freeze dried to constant weight, and the amounts of water and dry matter thus obtained. Sampling was done every 4 h during a 24 h period; eight or nine different trees were sampled at each sampling time and mean values were used to plot the graphs in Fig. 1. On the basis of the fresh sample weights, statistical analysis showed that: (1) for xylem, there are significant differences between times as compared with variation between trees within times; the average standard error of a mean is 1.0; (2) for phloem, the mean for 2400 h is significantly lower (1% level) than the mean of values at all other times, which do not differ significantly from each other; and (3) the difference between means for the two types of tissue is highly significant at 0400 h and at 2000 h, and not significant at other times; the average standard error of a difference between two means at a given time of day is 0.63.

On sampling days, meteorological data indicated that sunrise and sunset occurred at about 0510 h and 1900 h respectively. The days were partially cloudy, of high humidity (relative humidity >65%) and of moderate temperature with little wind, so that transpiration would not have been excessive.

During daylight active transpiration begins with a resultant increase of tensile forces, chiefly in the outermost vessels. The operation of these forces withdraws water from the developing tissues, those cells nearest to the vessels being the most affected (for example, ref. 2). The effects of these forces is far-reaching: Wilson *et al.*³ have shown that the water contents of leaves, stems and roots of herbaceous plants reach a minimum during the afternoon and attain a maximum during the night (see also refs. 4, 5). That is, the water stress would be greater in trees, for the developing stem tissues of the xylem than for those of the phloem. As a result of these conditions, the developing phloem tissues lose water at a slower rate (Fig. 1) than the developing xylary tissues (about 0500 h to 2000 h).

By comparison with the developing phloem tissues, the developing xylem tissues are still subject to a greater water stress at 2000 h. Hence between 2000 h and 2400 h the developing xylary tissues will rapidly withdraw water from the immediately adjacent developing phloem tissues until the water demand of the developing xylem tissues is moderated. Thereafter, all developing tissues will regain water as it becomes available, by way of the mature xylem vessels, from the root system of the tree. These indications support the deductions of Zahner¹ and other workers. The developing phloem tissues will regain their full complement of water at a later time than the developing xylem tissues because of their physical location within the bole of the tree.

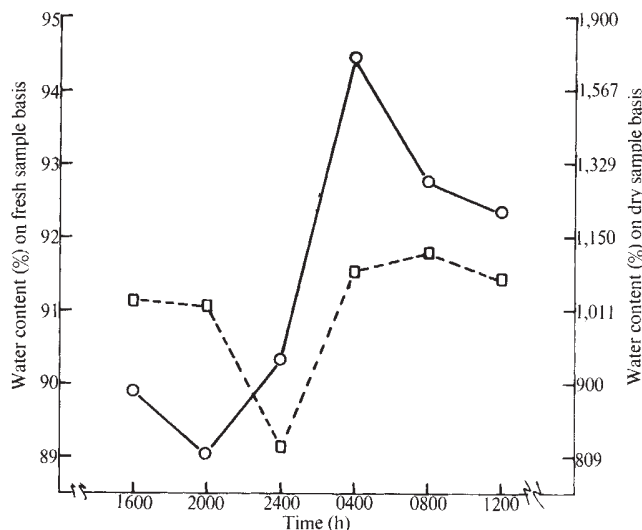


Fig. 1 Water content for developing tissues of *Eucalyptus regnans* tree stems. ○—○, Developing xylem tissue; □—□, developing phloem tissue.

If it is assumed that the dry matter, within the developing tissues of a tree stem, remains approximately constant in mass over a period of 24 h, then the samples of xylary tissues taken in the early morning contain about twice as much water as those collected during the late afternoon, early evening period (Fig. 1, right ordinate). These variations in water content imply that diurnal expansion and contraction of the developing cells take place, and may be of considerable physiological significance during the growth of developing secondary cells in a tree stem. Thus, changes in the concentrations of sugars and other soluble substances may be reflected in various interconversions between individual cytoplasmic materials, in the biosynthesis of cell-wall components and in other intra- or intercellular transformations (see also Zahner¹ and Kramer⁶).

We thank Mr K. J. Harrington, Mrs E. Zerdoner and Dr A. F. A. Wallis, of the Forest Products Laboratory, for help in collecting the samples; Miss N. Ditchburne, of the Division of Mathematical Statistics, for analysing the data obtained; and officers of the Forests Commission of Victoria for providing a sample plot of young eucalypt trees on Mt Dandenong, Victoria.

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- ¹ Zahner, P. J., *Water Deficits and Plant Growth* (edit. by Kozlowski, T. T.), 2, 191 (Academic Press, London and New York, 1968).
- ² Stewart, C. M., *Nature*, **214**, 138 (1967).
- ³ Wilson, C. C., Boggess, W. R., and Kramer, P. J., *Amer. J. Bot.*, **40**, 97 (1953).
- ⁴ Kozlowski, T. T., *J. Hort. Sci.*, **43**, 1 (1968).
- ⁵ Kozlowski, T. T., *Water Deficits and Plant Growth* (edit. by Kozlowski, T. T.), 1, 1 (Academic Press, London and New York, 1968).
- ⁶ Kramer, P. J., *Plant and Soil Water Relationships: A Modern Synthesis* (McGraw-Hill Book Company, New York, 1969).

Ancient Scythian Wool from the Crimea

THE origin of fine-woolled sheep has long interested historians and wool biologists. A fine-woolled type was recognized in antiquity, and one of us¹ showed that 2,000 yr old cloth from Palestine, although seemingly made of fine wool to the naked eye, contained a proportion of medium fibres revealed when

to the fifth century BC. It is interesting that it is associated with the Black Sea area, because the legend of the golden fleece, which has been taken to refer to fine wool, is of similar date and is associated with the same area. The only previous Scythian sample examined, from Parzirik in central Asia, was a hairy type with a fleece not unlike that of the sheep in the same area today⁶.

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- ¹ Ryder, M. L., *Nature*, **204**, 555 (1964).
- ² Ryder, M. L., *The Domestication and Exploitation of Plants and Animals* (edit. by Ucko, P. J., and Dimplebey, G. W.) (Duckworth, London, 1969).
- ³ Ryder, M. L., *Nature*, **240**, 355 (1972).
- ⁴ Ryder, M. L., and Stephenson, S. K., *Wool Growth* (Academic Press, London and New York, 1968).
- ⁵ Ryder, M. L., *Aust. J. Sci.*, **24**, 246 (1961).

Table 1 Fibre Diameter Measurements (μm)

	System	Diameter range*	Mode	Mean	Distribution	Coeff. of variation (%)	Standard deviation	Percentage medullated	Fleece type
Cloth	(a)	10-25, 29, 31, 35	16	16.5	Skew fine	24.2	4.0	0	Fine
	(b)	9-26	12	14.3	Skew fine	23.0	3.3	0	Fine
Yarn		8-24, 34, 44, 45	13	15.4	Skew fine	38.0	5.9	2	Fine

* Fibres outside the principal range are listed separately.

examined under the microscope. This predominant type at that time formed a generalized fleece in an intermediate evolutionary position between a more primitive hairy type and several modern more highly evolved fleece types, notably the true fine wool, which was already in existence in small numbers at that time^{1,2}.

The chief feature of this generalized type is a skewed distribution of fibre diameter, in which the bulk of the fibres is fine. It was in existence in the Danish Bronze Age¹ and in ancient Egypt³. The true fine wool has a symmetrical diameter distribution, with a mode and mean about 20 μm , and there are suggestions that this went back to the fourth century BC in Palestine².

The material comprised two pieces of cloth, one having only one yarn, in the Ashmolean Museum, Oxford, and came from a Scythian tomb (Tumulus I) in the Crimea near the Greek city of Nymphaeum. Its date is fifth century BC.

Whole-mount microscopical preparations were made and diameter measurements carried out on 100 fibres from each yarn using the International Standards Organization method 181 (ref. 4).

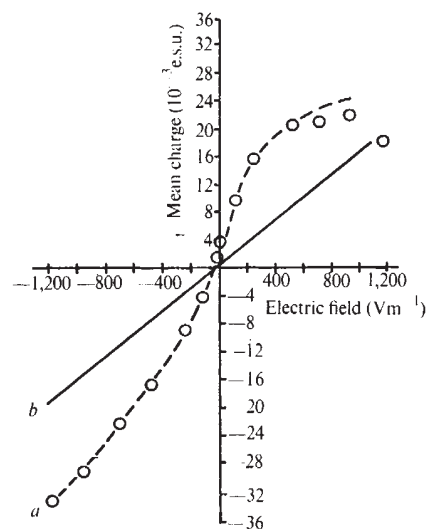
The wool fibres had the yellow-brown discoloration common in archaeological specimens with no evidence of the granules associated with natural pigmentation.

Fibre diameter measurements are shown in Table 1. The fleeces are clearly of fine type, although the diameters still have a skewed-to-fine distribution. The means and modes have an exceptionally low magnitude even for fine fleeces. These values are lower than those in the Egyptian wool³ and were found previously in Danish Bronze Age wool¹ and some Roman samples². The means and modes are comparable with the undercoat of the wild sheep². In spite of the fineness, a few of the fibres had a medulla. This has been noted previously in archaeological specimens, notably in the Egyptian wool³.

These samples firmly establish the fine wool as going back

Erratum

OWING to an administrative error, Fig. 2 was omitted from the article "Polarization Charging Effect and Thundercloud Electrification" by Zev Levin and W. D. Scott (*Nature*, **240**, 232; 1972).



In paragraph 4, line 4 and paragraph 5, line 1 therefore Fig. 1 should read Fig. 2. In paragraph 2, line 5 should include (Fig. 1) after 5,000 V m⁻¹.

BOOK REVIEWS

Linguistic Development

Sentences Children Use. By Paula Menyuk. Pp. xii + 165. (MIT: Cambridge, Massachusetts and London, May 1972.) \$1.95.

PSYCHOLOGISTS interested in the processes by which children acquire their native language have slowly come to the realization that an analysis of language behaviour in purely descriptive terms is inadequate. Part of Chomsky's revolution in linguistics was to show that grammar is generative—that the speaker's competence consists of rules which allow him to generate grammatically acceptable new combinations of words. If this approach is to be properly applied to child language studies, it will be necessary to analyse children's utterances in more depth and to produce structural descriptions which capture the abstract features which they code. In *Sentences Children Use*, Paula Menyuk states that her purpose is to describe the utterances of children at various developmental stages by "using the techniques of experimental psychology within the framework of a generative model of grammar". The book is devoted to a structural description of the sentences which a group of normal children produced and to a study of their responses in an imitation task. In addition, the utterances and imitations of a small group of linguistically deviant children are analysed.

Menyuk examines the development of both base structure and transformational rules. A case is made that even the early utterances of the child which consist of only single morphemes are nevertheless "sentences" since they are prosodically marked and because they are productively used. She represents these earliest sentences as: topic + intonational marker. Later, multi-morpheme utterances are similarly used generatively; the child does not simply imitate what he hears. This is well known to psycholinguists. What Menyuk adds, however, is a close analysis of the base structure rules. She finds that by the age of three years, all of the children in the normal group have expanded all of the nodes in the base structure, that is, they are able to produce utterances which express all

of the basic categories. This is in contrast to the transformational rules, not all of which are used by all of the normal children surveyed between three and seven years of age.

Another interesting method Menyuk used was to make a careful linguistic analysis of sentences the children produced which deviated from grammatically well-formed ones. Although one may question Menyuk's particular linguistic interpretations, the data are presented for the reader to see for himself, and these observations may prove extremely valuable to students of language who wish to examine the acquisition or development of particular linguistic features.

In spite of the claim to be using the methods of experimental psychology, only one "experiment" is reported: having children imitate both grammatical and deviant sentences actually taken from the production data. In the results, one finds more evidence of what others in the field have claimed—that imitation is not the method of acquisition. Children only imitated structures they were already spontaneously producing and occasionally structures which they were on the verge of acquiring in their productive speech. Furthermore, the length of a sentence was not a factor which determined successful imitation even for children as young as three years and even with sentences up to nine words in length. Structure, not length, determined whether a sentence was successfully imitated.

The same imitation task was administered to a group of children classified as "infantile" in their use of language. Unfortunately we are told very little about this group—how it was obtained, how the children were diagnosed, and how many children were tested. From her results, Menyuk concludes that these children are arrested at an early stage of language development, but one which differs qualitatively from normal-speaking children. She speculates that some kind of short term memory limitation may be responsible for their problems.

One drawback to this book is the inelegant and heavy style of writing. The terminology is unnecessarily convoluted, and explanations often take

too many connecting links for granted. This makes the book difficult to read and easy to misinterpret. The ungrammatical sentences children use nevertheless communicate; the sentences Menyuk uses too often do not. This is a shame, for the book is an important one for showing how a structural analysis can be made. If one can cope with its style, this book offers rewarding insights into the acquisition and development of language structure.

RICHARD F. CROMER

Joseph Henry

The Papers of Joseph Henry. Edited by Nathan Reingold. Assisted by Stuart Peirson, Arthur Molella, James Hobbs and John Kerwood. Vol. 1: December 1797–October 1832. Pp. xxxix + 496. (Smithsonian Institution: Washington, December 1972.) \$15.

To those historians who look for major contributions to modern science, nineteenth-century America cannot but seem an arid region. Americans made very few discoveries of important phenomena, or wide generalizations which brought into relationship facts which had previously seemed isolated. Exceptions to this generalization would include Joseph Henry who, independently of Faraday, discovered electromagnetic induction; and Willard Gibbs who introduced thermodynamics into chemistry. But as Americans themselves came to recognize, by the end of the nineteenth century America had become a dominant power in technology without yet emerging as a great centre of pure science. One might expect then that while filial piety might move those at the Smithsonian Institution to publish Henry's papers, the resulting volume would be of small interest to any but specialists. This would be quite wrong; for Nathan Reingold and his associates have produced a work which should be of great interest to all those concerned with science and its development. They have shown once again that there is no need for parish-pump history to involve Chauvinism or antiquarianism; but that on the contrary the close study of a scientist against his background can

illuminate the way science works, in ways that the enumeration of major contributions to modern science cannot.

The volume, the first of many, presents us with what the editors describe as "a broad documentary history of a period and a place, not merely a narrow recital of events in a career". They have drawn upon letters, diaries, lecture-notes, and minute-books; most but not all of which have immediate reference to Henry. Their aim is to show the growth of an American scientific community; an entity which was frequently appealed to by philosophers in nineteenth-century America, but which at the beginning of the century would have been hard to define. Benjamin Franklin had not founded a school, and the two leading scientists of the period of the Revolution, Count Rumford and William Charles Wells, had both gone to Europe. In succeeding volumes we shall no doubt see men of science coming to regard themselves as a community having common interests and purposes; but in this first volume, which ends with Henry, at the age of thirty-four, about to take up a Chair at Princeton, the nature of science and its relation with technology is the chief point at issue.

Here we find that though Henry, in an introductory lecture on chemistry printed here, speaks of the need for "speculative science", he and his contemporaries do not seem to have distinguished pure and applied science. The distinction Henry makes is between practice guided by genuine knowledge, and the mere empiricism of inventors. We find Henry himself advising industrialists on the magnetic separation of iron ore, and deploring patent laws which seemed to him to force scientists to make a choice between making their discoveries freely known, on the one hand, and profitable on the other. The emphasis on the applications of science which we find in these writings of Henry's is very like that in the lectures of his older contemporary, Humphry Davy, and does not in itself represent anything distinctively American. In the same way, "science" in America in the early years of the nineteenth century seems to have meant particularly natural history, geology, meteorology, and terrestrial magnetism; and it was from this last study that Henry moved on to electromagnetism. Mathematics were indeed cultivated, but it seems to have been the "mixed" or applied branch rather than higher mathematics. Very much the same situation prevailed in Britain, where critics of the *status quo* called for more support for mathematics from a government which was not ungenerous in its support of descriptive sciences; urging that applied mathematics could be the most useful of sciences.

Not only was the question of utility differently handled in Henry's day from the way it is in ours, but the boundaries between the various sciences were differently drawn. Thus when Henry made what were then the most powerful electromagnets in the world, the professors who urgently wrote asking for one to demonstrate before their classes wanted it for their chemistry lectures; and not, as we might expect, for the mathematics or natural philosophy classes. This again was not an American classification of sciences; Volta's discovery had shifted electricity into chemistry, and Faraday held office only in the chemical section of the British Association. There were distinctive features about the way science was carried on in America, but the great general questions seem to have been similarly handled on both sides of the Atlantic.

Henry's work on electromagnetism was done when he was professor of Mathematics and Natural Philosophy at the Albany Academy; and the documents tell us much about the functioning of this body. Again, it does not fit modern classifications, being neither a high school nor a college; it had some free places, one of which Henry got, and it prepared some students for college and others for a career. Henry, like Faraday, thus became a Professor without ever getting a first degree. Mathematics were regarded by the governing body of the Academy as perhaps the most important branch of knowledge taught there; and we find discussions of which textbooks should be prescribed, and what philosophical instruments were necessary. Albany also had an Institute, on the Napoleonic model, one "class" of which was devoted to science; in which Henry became a leading light. We find here the letters and minutes relating to Henry's appointments to Albany and Princeton, which have a certain fascination.

Henry's predecessor at Albany was sacked for being involved with a female of low character; Henry seems to have been immune from such temptations, to judge from what we find here of his life. We see his student notebooks, and a field-trip diary; his curiously formal letters to his cousin Harriet who became his wife, including some making up a row; other family letters; and letters illustrating his activities as a land-surveyor and then as a Professor. Even on his honeymoon he spent some time investigating scientific apparatus at Yale; earlier he had visited West Point Military Academy which, in the tradition of the *Ecole Polytechnique*, seems to have provided the best scientific training available at that time in America. In minutes and correspondence about the *Transactions* of the Albany Institute and Silliman's *Ameri-*

can Journal of Science, we learn much about the dissemination of science at this time; and see Henry and Silliman working out demonstration experiments in their correspondence. We also see Henry being prickly about his priority, and about the amount of credit due to his co-worker, Philip Ten Eyck.

We must then congratulate the editors on their selection, and the publishers on producing the book handsomely at what is by today's standards a low price; and look forward to the volumes to come. The notes and index will provide a valuable "who's who" for students of American science; and we see Joseph Henry the man against a rich background. DAVID KNIGHT

About the Ultrapure

Ultrapurity: Methods and Techniques. Edited by Morris Zief and Robert Speights. Pp. xv+699. (Marcell Dekker: New York, June 1972.) \$37.50.

EDITORS who attempt to cover ultrapurity in a single book, even a big book, must of necessity be bold and the magnitude of the task can be gauged from the appendix (fifty-three pages) entitled "Information Sources for Ultrapurification and Characterization" which, although it gives incomplete coverage, lists fifty-two information centres and twenty-three journals concerned with purification.

Zief and Speights in a short preface to the twenty-two chapters provided by twenty-four authors claim that the book brings together for the first time the preparation, handling, containment and analysis of ultrapure materials. There is no general introduction nor summary so that neither the philosophy underlying ultrapurification nor the condition necessary for the establishment of purity is discussed.

The book opens with a discussion on the preparation of samples of alkali halides suitable for use as optical components, scintillation counters and solvents and the next chapter deals with the production by frontal-analysis chromatography of specimens of organic solvents for ultraviolet spectroscopy. As the author of the chapter on pure sodium and potassium is employed by Atomics International presumably the samples of these metals are intended for use in the atomic energy field. The sublimation of phosphorus pentoxide is described for the production of low-cost specimens which can be resublimed without the formation of a residue and can be used for the preparation of ultrapure orthophosphoric acid. The chapter on the purification of proteins by membrane ultrafiltration depicts equipment for the removal of salts and of certain proteins

provided they differ sufficiently in properties. Short chapters on the purification of *p*-xylene by partial freezing and on the purification of isopropylbenzene by preparative gas-liquid chromatography record the processing of relatively small samples. The discussion on fractional distillation (nineteen pages) emphasizes the steps which must be taken to protect the samples against contamination by the atmosphere. The author of the account of dry-column chromatography expresses the hope that workers will begin to use this technique. The importance of the nature of the impurities in the starting material for the preparation of pure water is emphasized and the production of specimens of low electrical conductivity and for use in the electronics industry are considered. The difficulties in the preparation of pyrogen-free and particle-free water are mentioned and the chapter closes with the statement, "Ultrapure macroscopic water can be considered to contain microparticles based on the isotopes of hydrogen and oxygen". However, changes in isotopic composition of water during purification are not discussed and the preparation of samples of precise density is, therefore, not reported. There is a straightforward account of the purification and analysis of cholesterol.

The section on "Handling" and "Containment" would have been better written under a single heading because the chapter "Contamination Problems in Trace-Element Analysis and Ultrapurification" presents useful information on storage vessels which is covered again in a slightly different form in the chapters "Glass Containers for Ultrapure Solutions" and "Vitreous Silica". A reader of "Airborne Contamination" would have to look elsewhere for details but is provided with only nine references for this purpose. The chapter entitled "Ceramics" discusses eighteen ceramics in nine pages.

The twenty-four page chapter on "High-Purity Chemicals—A Challenge to Practical Analysis" summarizes briefly the determination of major and minor constituents and is written from much first hand experience. The titles of chapters on "Emission Spectroscopy", "Flame Spectrophotometric Trace Analysis", "Neutron-Activation Analysis", "Visible Spectrophotometry" and "Coulometric Titration" sufficiently indicate their contents.

Much tabulated data is given but the quality of presentation is very uneven; some chapters are difficult to read and are incomprehensible in places due to errors—for example, "A good syringe pump, set at the optimum flow rate, is invaluable for ironing and partial clogging and airflow inconsistencies".

The book jacket states that "This work is directed to all those working in research, development, or analysis of ultrapure products—electronic engineers, analytical chemists, clinical chemists, geochemists, oceanographers, material scientists, and environmental researchers". In my opinion this volume of loosely coordinated chapters attempts too much and as a result many workers in the above mentioned fields may decide to follow the advice given to analysts on page 527, "Specialized applications to specific problems must be sought in sources best known to the individual analyst". Unfortunately most applications of ultrapurity are specialized. E. F. G. HERINGTON

Air Pollution

Air Pollution. By W. L. Faith and A. A. Atkisson. Second Edition. Pp. viii + 393. (Wiley: New York and London, December 1972.) £8.65.

WHEN I edited a book with the same title in 1957, public enemy number one, from the point of view of air pollution, was the coal fire, and number two grit and coarse dust, for example, from chain grate stokers. This book illustrates the fact that, in Europe as well as in the USA, public enemy number one is now the internal combustion engine, and number two is SO₂. The oxides of nitrogen can undergo a photochemical reaction with unburnt hydrocarbons in conditions of intense sunlight and long standing inversions, and so the car is blamed for the Los Angeles smog and a whole chapter is devoted to photochemical air pollution. The CO and unburnt and partially burnt hydrocarbons given off by the car are a consequence of bad combustion and so high fuel consumption, whereas, on the contrary, oxides of nitrogen are primarily a consequence of high combustion temperatures and excess combustion air, while lead is emitted because its addition to the fuel provides a cheap way of operating high power compact engines on a large fraction of the total petroleum.

This second edition is changed from the first edition of 1959 in several ways. First, there is an increase in the emphasis on tall stacks, the use of which reduces the local maximum ground level concentration by spreading it further away, but is not a final solution to the problem when there are enough stacks in a region to combine their long distance effects. The main formulae for dispersion were available 15 years ago, but more work is recorded on effects of tall buildings, irregular terrains, inversions, "fumigation" and multiple stacks. Second, an account of the development of air quality standards and emission regulations in the USA is

added. Then automobile exhaust in the earlier edition has been extended to cover vehicle testing on chassis dynamometer, pollution control methods, two pages only on diesel exhausts and two on aircraft emissions.

The chapter on "Social Origins of Air Pollution" takes what one can call a five-year forward legal-economic look, but completely fails to take account of what the rest of the world can see, that there is no real solution to the pollution and other problems as long as the USA continues to base its economy on a fuel and other resource consumption which is six times the world average. Pollution Control, treated as a problem in isolation from others, can only lead to such results as the US proposed standards for car exhaust emission, causing the manufacturers to fit afterburners and exhaust gas recyclers which cause an increase in the fuel consumption and the engine size and the effective use of which cannot be ensured for long after the car is used. M. W. THRING

Degree of Belief

Probability, Induction and Statistics: The Art of Guessing. By Bruno de Finetti. Pp. xxiv + 266. (Wiley: New York and London, November 1972.) £6.50.

DE FINETTI is perhaps the most brilliant worker in the field of probability this century. His work is little known in Britain because he writes mainly in rather difficult Italian, and because he does not publish in statistical journals, where the main operational material on probability has appeared. Here we have the opportunity to read, in English, about some of his ideas. No one interested in probability should fail to read this book.

His view of probability is that it is always "a measure of the degree of belief of a given subject in the occurrence of an event (proposition)". The book is not written as a unit, but consists of eleven papers divided into three main groups. The first group consists of papers on the operational foundations. His philosophical attitude is essentially behaviouristic, and probability is measured and understood by the subject's attitude to decision problems. In these papers he discusses, amongst other things, how this measurement might be performed. Statisticians who keep saying the prior distribution is unknown should read this section. The next group of papers is concerned with the axiomatic foundations of probability: in particular, whether it is finitely or σ -additive. This section is really only suitable for the reader equipped with the necessary technical knowledge of measure theory. Frankly it leaves me

unimpressed, for it seems to depart from the operational standards of the rest of the book. How, for example, can you choose an integer at random? Such a choice is at the root of the axiomatic difficulties.

The third section is devoted to induction and statistics, not in a narrow, technical sense but in the widest meanings of these terms. Adherents of the subjectivistic view of probability have been slow (and perhaps a little surprised?) to appreciate the catastrophic effect their ideas have on the practical problems of science. All scientists who are interested in the methodology of science could read parts of this section with profit.

The translation has not been well done and de Finetti's meaning is not always transparent. But this is an important book and should not be passed over on that account.

D. V. LINDLEY

Freudian Controversy

Fact and Fantasy in Freudian Theory. By Paul Kline. Pp. x+406. (Methuen: London, January 1972.) £5.

THE controversy about the place of Freud's thoughts in general psychology shows no sign of abating. It is largely maintained not by psychoanalysts, who unfortunately and in contrast to Freud show now all too little interest in general psychology, but by efforts at refutation and more or less bad tempered attacks from academic psychologists. In this situation Paul Kline's book is particularly welcome because it breaks away from this traditional pattern. Kline is an academic psychologist with high standards of scholarship, competence in research methodology and fully conversant with Freud's work—in itself a rare combination. Each chapter of his book is devoted to a study of the "objective scientific evidence" relevant to one of the basic postulates in psychoanalytic theory. Kline begins with a concise definition of the postulate, citing chapter and verse from Freud which enhances the book's value as a reference work; he then discusses the general methodological problems of research in that area and presents in schematic detail the empirical work with his own critique of its methodological adequacy. While Kline cites well over 600 references, he acknowledges that this is not comprehensive, and it would be churlish to cite omissions. He finds experimental support for some major Freudian concepts, such as repression, and certain personality constellations even though their aetiology in childhood remains unconfirmed.

Many experimenters have demonstrated remarkable ingenuity in devising

testable hypotheses from psychoanalytic theory and designing situations in which they could be investigated. There is, for example, the well known work of Hall who submitted the manifest dream content of men and women to statistical analysis which lent strong support to the idea of an Oedipal complex and castration anxiety even though he had of course no access to what Freud regarded as essential, namely the latent dream content. This work certainly refutes the notion that dreams are the result of randomly firing nerve cells. The situation is less satisfactory with regard to another central part of the theory—some defence mechanisms. Kline rightly emphasizes that the methodological difficulties here are nearly insurmountable. Take, for example, projection, a concept for which there is a very large amount of clinical evidence and which has such widespread face validity that it has become accepted outside the technical jargon of the theory. Notwithstanding some efforts the experimental evidence for the mechanism is just not good enough. The crux of the difficulty is of course the experimental approach to the concept of the unconscious. The thief who cries "Stop, thief" is projecting as a deliberate purposeful disguise but not in the sense of the Freudian defence mechanism which requires that the motivation for projection be inaccessible to consciousness. One can take it from Kline that this discrimination is beyond the power of current research methods. Whether the unconscious should therefore be eliminated from psychology as a science, much as the one-time useful fiction of phlogiston was dropped, or whether it should, as Foucault seems to suggest, be regarded as the necessary identification of a border-line beyond which science cannot proceed, or whether clinical evidence should finally achieve scientific status within a framework of research which is concerned with meaning rather than mechanisms, is a question that Kline does not raise. In his careful and cautious fashion he lets the matter rest with stating that projection has not been experimentally established.

Where Freudian propositions are experimentally supported, Kline, in an effort at reconciliation with academic psychology, examines relevant predictions from theories of learning and concludes "that in most cases the Freudian phenomena could be fitted into a model derived from theories of learning but that these theories on their own could not have predicted the clinical observations. . . . So, far from regarding learning theory models and psychoanalytic theory as opposed, we consider them to be closely related—the Freudian theory supplying the details of the learning procedures". Much as one would like a

rapprochement, this suggestion may throw out the baby with the bathwater.

Notwithstanding the excellence of Kline's search for evidence, the value of many of his careful and critical comments and the usefulness of his book for reference purposes, one is left with a feeling that some of the major challenges which psychoanalysis presents to academic psychology have been avoided rather than elucidated.

MARIE JAHODA

Solar System Guide

The Solar System. By Z. Kopal. Pp. 152+14 plates. (Oxford University: Oxford, London and New York, January 1973.) £2.25 cloth; £1 paper.

OUR knowledge of the solar system has advanced by leaps and bounds during the last decade. For example, twelve men have walked on the surface of the Moon and spacecraft have photographed in detail the craters, volcanoes, mountains and valleys of Mars. In the next decade many more ambitious projects are planned. Spacecraft will start out on their journeys to Jupiter and Saturn, others will be soft landing on Mars to search the surface for traces of life. By 1975 the Skylab should be set up and man will at last be able to cast off the atmospheric cloak that continuously hampers ground based observations.

All these past achievements have been fully covered by the news media and in consequence a great deal of interest and enthusiasm has been engendered among the nonscientific members of the public. Now in all new fields a guide is needed if we are to get the maximum benefit from our travels. This is exactly what this book sets out to be—a guide to the solar system. In the introduction it states that its aim is to summarize for the nontechnical reader the principal features of our present knowledge of the astronomy, physics and chemistry of the solar system.

It succeeds admirably. Zdeněk Kopal must be congratulated on writing an excellent book, a book which was a joy to read and which takes us on a fascinating tour of our neighbouring planets. It breaks away from the old fashioned approach of treating every planet as a separate entity and instead stresses the important similarities and differences between the members of the solar system. Comparisons are even made between our solar system and the possible planetary companions of nearby stars. It is also up to date, containing details of the latest Apollo, Mariner and Venera results.

I would like to congratulate Professor Kopal on a job well done and to wish his book the great success that it deserves.

DAVID W. HUGHES

CORRESPONDENCE

Citation and Distinction

SIR,—I previously indicated¹ that frequency analyses of the *Science Citation Index* could help forecast Nobel Prize winners. A number of people have pooh-poohed this simple technique. Consequently, it is of interest to note that all of this year's Nobel Prize winners again were among the list of most frequently cited authors. Two of them were anticipated in my article, in which I gave a list of the fifty most cited authors for 1967, using the 1967 *SCI* as the data base. We have, since then, used the annual *SCIs* from the years 1961 through 1971 (except 1962 and 1963 which were not available then) to compile a list of most frequently cited authors. Out of more than 1.8 million authors cited, only 42,000 were cited at least thirty times in a single year during this nine-year period. However, less than 2,100 were cited more than 1,000 times. In this list will be found all of the Nobel Prize winners for 1972 and also winners for the preceding five-year period with few exceptions. Thus, the Nobel Prize winners were members of an elite group consisting of the top 0.1 per cent of all cited authors.

If any of your readers can propose another algorithmic procedure for measuring scientific impact, let him come forward. In the meantime, if scientific journalists, among others, wish to know where the action was, is, and will be, they would do well to look into this method. We recently used a similar technique to determine the relative "impact" of journals². In spite of the snide remarks of those³ who prefer the world of subjectivity, the latter study has caused a considerable amount of soul searching amongst those seeking a rationale for thousands of infrequently cited journals.

Yours faithfully,

EUGENE GARFIELD

*Institute for Scientific Information,
325 Chestnut Street,
Philadelphia, Pennsylvania 19106*

¹ Garfield, E., *Nature*, **227**, 669 (1970).

² Garfield, E., *Science*, **178**, 471 (1972).

³ Anonymous, *New Scientist*, **56**, 464 (1972).

Reprint Distribution

SIR,—The letter from Dr L. G. Johnson¹ prompts me to take up the problem of reprint requests from the point of view of the author.

I recently described a modification² of a widely used method³ for measuring

protein concentration. After the title had appeared in *Current Contents* the initial trickle of reprint requests swelled to a torrent and passed the 2,500 mark before subsiding to the present one or two per day. In my paper I attempted to balance the advantages of my method against its procedural disadvantages. Yet how many requesters, before writing, saw my paper and assessed whether the new method might on balance be useful? At most about 15 per cent since this group copied my mailing address from the paper. The remaining requests carried (to the despair of the Cambridge Post Office) the address given in *Current Contents*.

Since I could not supply everybody I gave the 15 per cent first priority. This is rough justice since my paper was presumably accessible to this group. On the other hand, it was no doubt inaccessible to many among the 85 per cent. Here I have in mind workers in undeveloped and scientifically underprivileged countries. These became my second priority.

Dr Johnson refers to possible mistaken impressions about working conditions of American scientists. In my view the prevailing impression is not that they are cushioned, by computer-based retrieval systems, so escaping the day-by-day work of reading through the literature, but rather that too many Americans (and too many non-Americans) restrict their reading to published contents lists and to the reprint request system even when, in many cases, adequate libraries and copying facilities are close at hand.

Because of his isolation Dr Johnson asks not to be numbered among the abusers of the reprint system. However, the extent of his isolation may not be widely recognized. I would suggest that his form of request include the information that the alternative to receipt of a reprint is a slog through hundreds of miles of Injun territory. The ubiquity of the Hollywood western would ensure a favourable reply to every request.

Yours faithfully,

E. F. HARTREE

*ARC Unit of Reproductive
Physiology and Biochemistry,
307 Huntingdon Road,
Cambridge CB3 0JQ*

¹ Johnson, L. G., *Nature*, **242**, 143 (1973).

² Hartree, E. F., *Analyt. Biochem.*, **48**, 422 (1972).

³ Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J., *J. Biol. Chem.*, **193**, 265 (1951).

Grafting Neologisms

SIR,—Biomedical vocabulary, specialized for centuries, expands with our knowledge. *Symbiosis* ("living together") connotes an intimate physical and physiological relationship between two organisms. *Prosthesis* ("placing onto") describes attachment of devices to increase comfort, health, or convenience: false teeth, artificial limbs, and so on.

Recently, machines that sustain essential life functions have been developed. Kidney machines clean blood of wastes when natural kidneys fail; heart-lung machines oxygenate and circulate blood during heart surgery. Soon a new type of device, artificial hearts, will be available. (These devices have already been tested successfully in calf, dog and baboon).

A seminar here has considered issues of technological assessment and moral evaluation of such devices as an artificial heart. We noted a lack of clear terms to describe relationships involving such technologies. "Man-machine symbiosis" is inadequate, since it implies two living partners. Machines are not properly candidates for symbiosis; they fulfil physiological needs but are not themselves living. They exist solely for service to their organism-associates, which in turn depend upon them for life, and not simply for comfort or convenience.

I submit to you and your readers two neologisms, hopefully useful for discussion of these organism-mechanism relationships—relationships promising increasing importance in future centuries of biotechnics.

Firstly, *epallobiosis* (ēp-āl'ō-bi-ō'sis; *epallobiotic*, adj.) refers to the dependency of an organism on an external life-support system, e.g., the already well known heart-lung and kidney machines.

Secondly, *enthetobiosis* (ēn-thēt'ō-bi-ō'sis; *enthetobiotic*, adj.) captures the relationship of "life dependent upon intoplasting" of a mechanical device (implant). The prefix *ep-*, emphasizing dependency, would here overburden pronunciation; context will suffice to imply relationship that is not casual but critical.

Yours faithfully,

ROBERT ROGER LEBEL

*The Jesuit School of Theology at
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California 94709*

Announcements

Erratum

IN the article "Radio Sources identified with Optical Objects using Precise Radio and Optical Positions" by H. Gent *et al.* (*Nature*, **241**, 261; 1973), line 10, paragraph 6, should read "The counts quoted in ref. 1 show that the probability of finding a stellar object of neutral colour brighter than 20 mag in the combined error regions for the 11 sources is only 1 in 50".

Corrigendum

IN the article "Cigarette Smoke: Effect of Aqueous and Nonaqueous Fractions on Mitochondrial Function" by C. Gairola and M. I. H. Aleem (*Nature*, **241**, 287; 1973), the cigarettes referred to are the 1R1 University of Kentucky Research Cigarettes and not IRI research cigarettes.

International Meetings

April 30–May 2, **Instrumentation in Vacuum Processes.** (Meetings Officer, The Institute of Physics, 47 Belgrave Square, London SW1.)

May 1–2, **Molecular Weights of Industrial Polymers.** (Dr R. Dietz, Division of Chemical Standards, National Physical Laboratory, Teddington, Middlesex.)

May 2–6, **Protides of the Biological Fluids.** (Simon Stevin Instituut, Jerusalemstraat 34, B-8000 Brugge, Belgium.)

May 3, **The Role of Sulphur Dioxide in Food Processing.** (Society for Chemical Industry, 14 Belgrave Square, London SW1.)

May 3–4, **Minicomputer Interfacing.** (Lisa Spaducci, Polytechnic of Central London, 115 New Cavendish Street, London W1.)

May 4, **Applied Functional Analysis in Teaching and Research.** (Secretary, The Institute of Mathematics and Its Applications, Maitland House, Warrior Square, Southend-on-Sea.)

May 5–12, **Food Group Annual Tour.** (Mr P. O. Dennis, Brooke Bond Oxo Limited, Witneys Technical Centre, Trojan Way, Purley Way, Croydon, Surrey.)

May 7–9, **Tenth Annual Rocky Mountain Bioengineering Symposium.** (N. B. Kinding, Dept of Electrical Engineering, University of Colorado, Boulder, Colorado 80302.)

May 8, **International Symposium on Crop Protection.** (Secretary, Faculteit van de Landbouwwetenschappen, Coupure Links 533, B-9000 Gent, Belgium.)

May 8, **The Application of Agricultural Science and Technology to Development.** (Assistant Secretary, Society of Chemical Industry, 14 Belgrave Square, London SW1.)

May 8–9, **Fluvial Processes and Sedimentation.** (Dept. of Extension, The University of Alberta, Edmonton, Alberta.)

May 9, **Chemical Engineering Contribution to Medicine and Health Care.** (Mr R. Mason, Institution of Chemical Engineers, 16 Belgrave Square, London SW1.)

May 13–18, **The International Congress on Noise as a Public Health Problem.** (Office of Noise Abatement and Control, US Environmental Protection Agency, Washington DC 20460.)

May 14–18, **Second Australian Symposium on Analytical Chemistry.** (Mr L. S. Dale, Australian Atomic Energy Commission, Research Establishment, Private Mail Bag P.O. Sutherland, NSW 2232, Australia.)

May 14–17, **Fifth International Course on**

Transplantation. (Dr R. Triau, 17 Boulevard des Belges, Lyon 69003, France.)

May 14–21, **The Use of Artificial Satellites for Geodesy and Geodynamics.** (Professor George Veis, National Technical University, Athens 147, Greece.)

May 15, **Radiationless Transitions in Aromatic Molecules.** (Dr O. L. J. Gijzen, The Royal Institution, 21 Albemarle Street, London W1.)

May 17, **Mathematics in Marketing.** (Secretary, The Institute of Mathematics and Its Applications, Maitland House, Warrior Square, Southend-on-Sea.)

May 17–19, **The Future of Scientific and Technical Journals.** (Program Chairman, John Phillips, Bldg. 2–8 RCA, Camden, New Jersey.)

May 18, **Specific Cell Adhesion.** (Dr R. C. Hughes, National Institute for Medical Research, Mill Hill, London.)

May 23, **Cancer Care—Assessment of the Present Position.** (Mr P. A. Sturgess, Assistant Secretary, Marie Curie Memorial Foundation, 124 Sloane Street, London SW1.)

May 24, **Anaesthesia in Laboratory Animals.** (Secretary, Dr R. J. Ward, Carworth Europe, Huntingdon Research Centre, Huntingdon.)

May 25–26, **New Developments in Diagnosis and Treatment.** (Allegheny General Hospital, 320 East North Avenue, Pittsburgh, Pa. 15212.)

May 28–30, **Second Scientific Congress at Istanbul.** (Professor Dr E. T. Cetin, General Secretary, Medical Faculty, Dept. of Microbiology, Tropical Diseases and Parasitology, The University, Istanbul.)

May 30–June 1, **The Use of Low Energy Accelerators.** (The Meetings Officer, The Institute of Physics, 47 Belgrave Square, London SW1.)

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